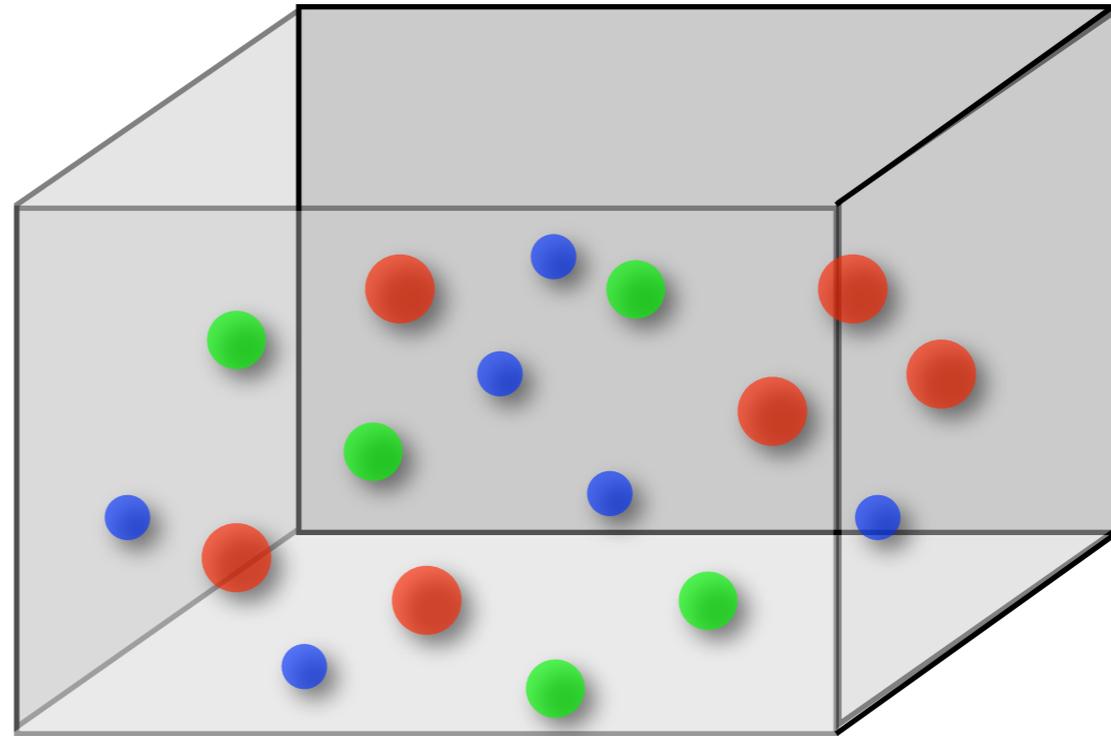


# Stochastic Chemical Kinetics

# Formulation of Stochastic Chemical Kinetics

Gillespie, Physical A, 1992

Reaction volume =  $\Omega$



## Key Assumptions

**(Well-Mixed)** The probability of finding any molecule in a region  $d\Omega$  is given by  $\frac{d\Omega}{\Omega}$ .

**(Thermal Equilibrium)** The molecules move due to the thermal energy. The reaction volume is at a constant temperature  $T$ . The velocity of a molecule is determined according to a Boltzmann distribution:

$$f_{v_x}(v) = f_{v_y}(v) = f_{v_z}(v) = \sqrt{\frac{m}{2\pi k_B T}} e^{-\frac{m}{2k_B T} v^2}$$

# Probability of Collision: Two Specific Molecules

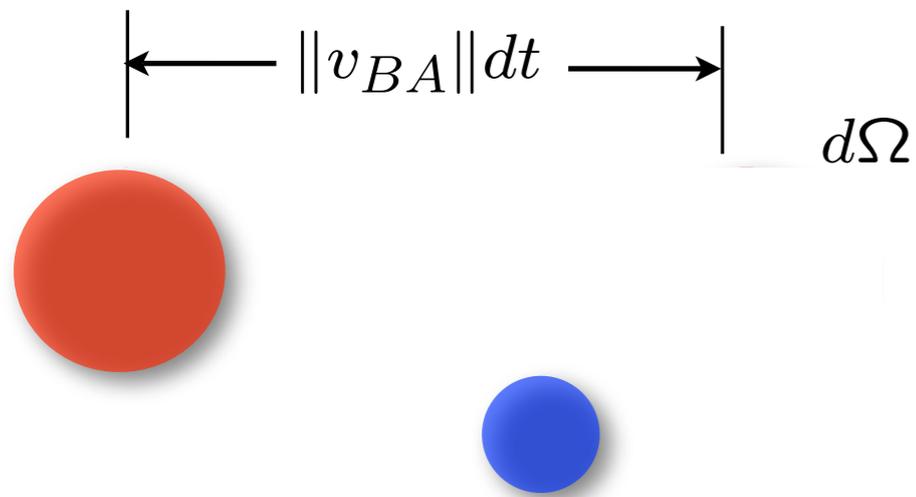
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## Given:

- Two spheres  $A$  and  $B$  with velocities  $v_A$  and  $v_B$ , and radii  $r_A$  and  $r_B$ .
- The probability that the center of either sphere lies in a volume  $d\Omega$  is given by  $\frac{d\Omega}{\Omega}$ .

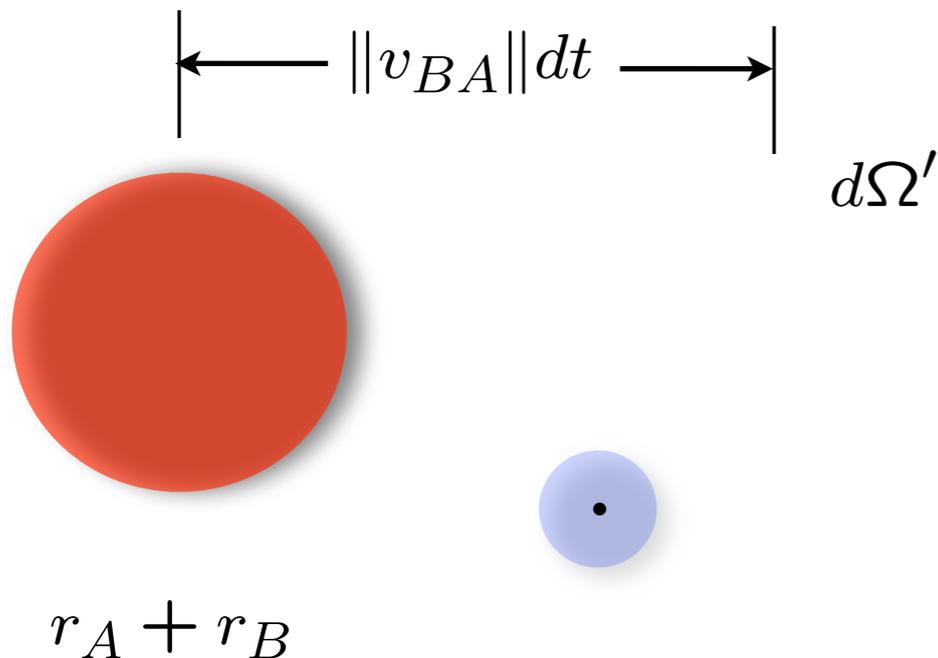
What is the probability that  $A$  and  $B$  will collide in the time  $[t, t + dt]$ ?



In the time  $[t, t + dt]$  molecule  $A$  sweeps a volume of  $d\Omega = \pi r_B^2 \|v_{BA}\| dt$

Collision takes place if *any part of A* lies in the region  $d\Omega$ .

### Equivalently ...



During  $[t, t + dt]$  a molecule with radius  $r_A + r_B$  sweeps a volume of  $d\Omega' = \pi (r_A + r_B)^2 \|v_{BA}\| dt$

Collision takes place if *the center of A* lies in the region  $d\Omega'$ .

**The probability of  $A$  and  $B$  colliding during  $[t, t + dt]$  is**

$$\frac{1}{\Omega} \pi (r_A + r_B)^2 \|v_{BA}\| dt$$

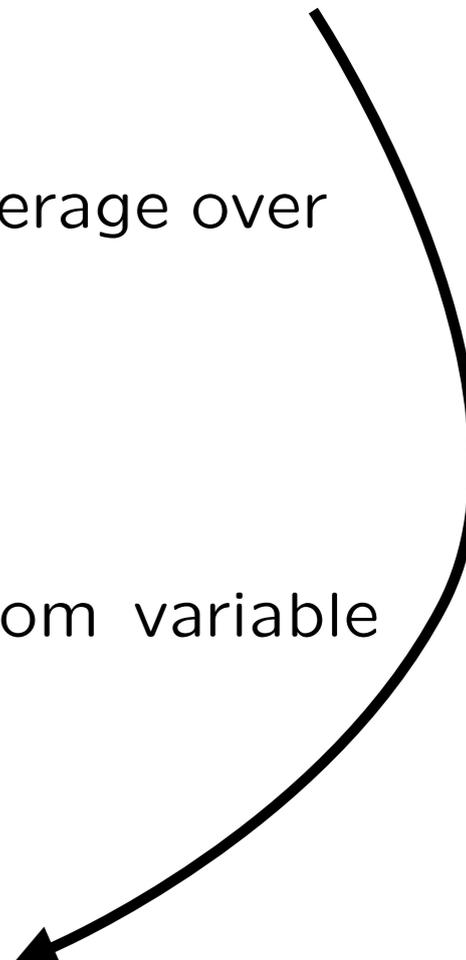
## Note:

- The probability of  $A$  and  $B$  colliding was computed for a *given a relative velocity of  $v_{BA}$*  (conditional probability)
- The relative velocity is a *random variable*, and we must average over all velocities.

If we denote by  $f_{BA}(\cdot)$  the probability density of the random variable  $V_{BA}$  we have

$$\begin{aligned} \text{Collision Probability in } [t, t+dt] &= \int_{\mathbb{R}^3} P(\text{collision in } [t, t+dt] \mid V_{BA} = v) f_{BA}(v) dv \\ &= \int_{\mathbb{R}^3} \frac{1}{\Omega} \pi (r_A + r_B)^2 \|v\| dt f_{BA}(v) dv \\ &= \frac{1}{\Omega} \pi (r_A + r_B)^2 dt \int_{\mathbb{R}^3} \|v\| f_{BA}(v) dv \end{aligned}$$

mean relative speed



The probability density function of  $f_{BA}(\cdot)$  can be easily computed from the Boltzmann distribution of the velocity and the independence of  $V_x$ ,  $V_y$ , and  $V_z$ .

$$f_{BA}(v) = \left( \frac{\hat{m}}{2\pi k_B T} \right)^{3/2} e^{-\frac{\hat{m}}{2k_B T} \|v\|^2}, \quad \text{where } \hat{m} = \frac{m_A + m_B}{2}$$

Hence

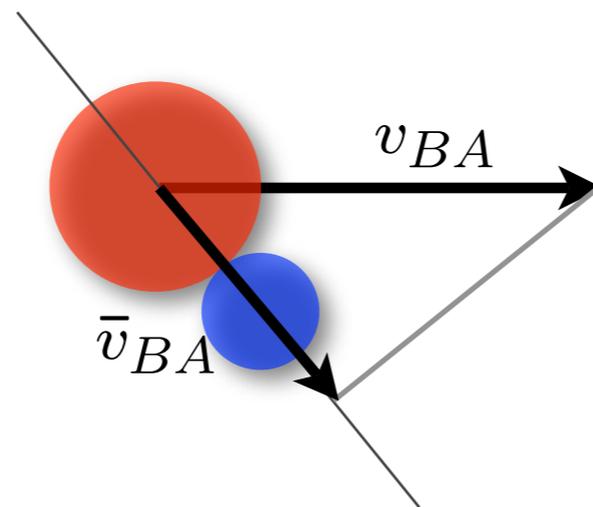
$$\begin{aligned} \text{Mean relative speed} &= \int_{\mathbb{R}^3} \|v\| f_{BA}(v) dv \\ &= \int_{\mathbb{R}^3} \|v\| \left( \frac{\hat{m}}{2\pi k_B T} \right)^{3/2} e^{-\frac{\hat{m}}{2k_B T} \|v\|^2} dv \\ &= \sqrt{\frac{8k_B T}{\pi \hat{m}}} \end{aligned}$$

**Probability of A-B collision within  $[t, t+dt]$ :**

$$\frac{1}{\Omega} \pi (r_A + r_B)^2 dt \sqrt{\frac{8k_B T}{\pi \hat{m}}}$$

Not all collisions lead to reactions. One can factor in the "reaction energy".

**Assumption:** An  $A - B$  collision leads to a reaction only if the kinetic energy associated with the component of the velocity along the line of contact is greater than a critical energy  $\epsilon$ .



Reaction if  $\frac{1}{2}\hat{m}\bar{v}_{BA}^2 > \epsilon$

It can be shown that:

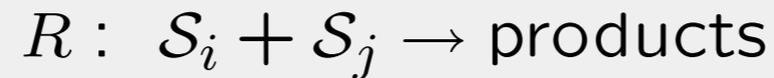
$$\text{Probability (A-B reaction | A-B collision)} = e^{-\frac{\epsilon}{k_B T}}$$

**Probability of A-B reaction within  $[t, t+dt]$ :**

$$\frac{1}{\Omega} \pi (r_A + r_B)^2 \sqrt{\frac{8k_B T}{\pi \hat{m}}} e^{-\frac{\epsilon}{k_B T}} dt$$

Given  $N$  species:  $\mathcal{S}_1, \dots, \mathcal{S}_N$  with populations  $x_1, \dots, x_N$  at time  $t$ .

Consider the bimolecular reaction channel (with distinct species):



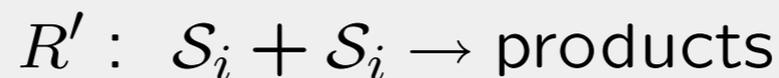
The number of distinct  $\mathcal{S}_i - \mathcal{S}_j$  pairs that can react is:  $x_i \cdot x_j$ . Therefore,

**Probability of an  $R$  reaction within  $[t, t+dt]$ :**

$$x_i x_j \frac{1}{\Omega} \pi (r_i + r_j)^2 \sqrt{\frac{8k_B T}{\pi \hat{m}}} e^{-\frac{\epsilon}{k_B T}} dt = w(x)$$

$w(\cdot)$  is called the **propensity function**.

Consider the bimolecular reaction channel (with same species):



The number of distinct  $\mathcal{S}_i - \mathcal{S}_i$  pairs that can react is:  $\frac{x_i(x_i-1)}{2}$ . Therefore,

**Probability of an  $R'$  reaction within  $[t, t+dt]$ :**

$$\frac{x_i(x_i-1)}{2} \frac{1}{\Omega} \pi r_i^2 \sqrt{\frac{8k_B T}{\pi \hat{m}}} e^{-\frac{\epsilon}{k_B T}} dt = w(x) dt$$

# Reactions and Propensity Functions

Reaction	Propensity $w(x)$	Rate $c$
$\phi \xrightarrow{c} \text{Products}$	$c$	$k\Omega$
$S_i \xrightarrow{c} \text{Products}$	$c \cdot x_i$	$k$
$S_i + S_j \xrightarrow{c} \text{Products}$	$c \cdot x_i x_j$	$\frac{1}{\Omega} \pi (r_i + r_j)^2 \sqrt{\frac{8k_B T}{\pi \hat{m}}} e^{-\frac{\epsilon}{k_B T}}$
$S_i + S_i \xrightarrow{c} \text{Products}$	$c \cdot \frac{x_i(x_i - 1)}{2}$	$\frac{4}{\Omega} \pi r_i^2 \sqrt{\frac{8k_B T}{\pi \hat{m}}} e^{-\frac{\epsilon}{k_B T}}$

For a monomolecular reaction:  $c$  is numerically equal to the reaction rate constant  $k$  of conventional deterministic chemical kinetics

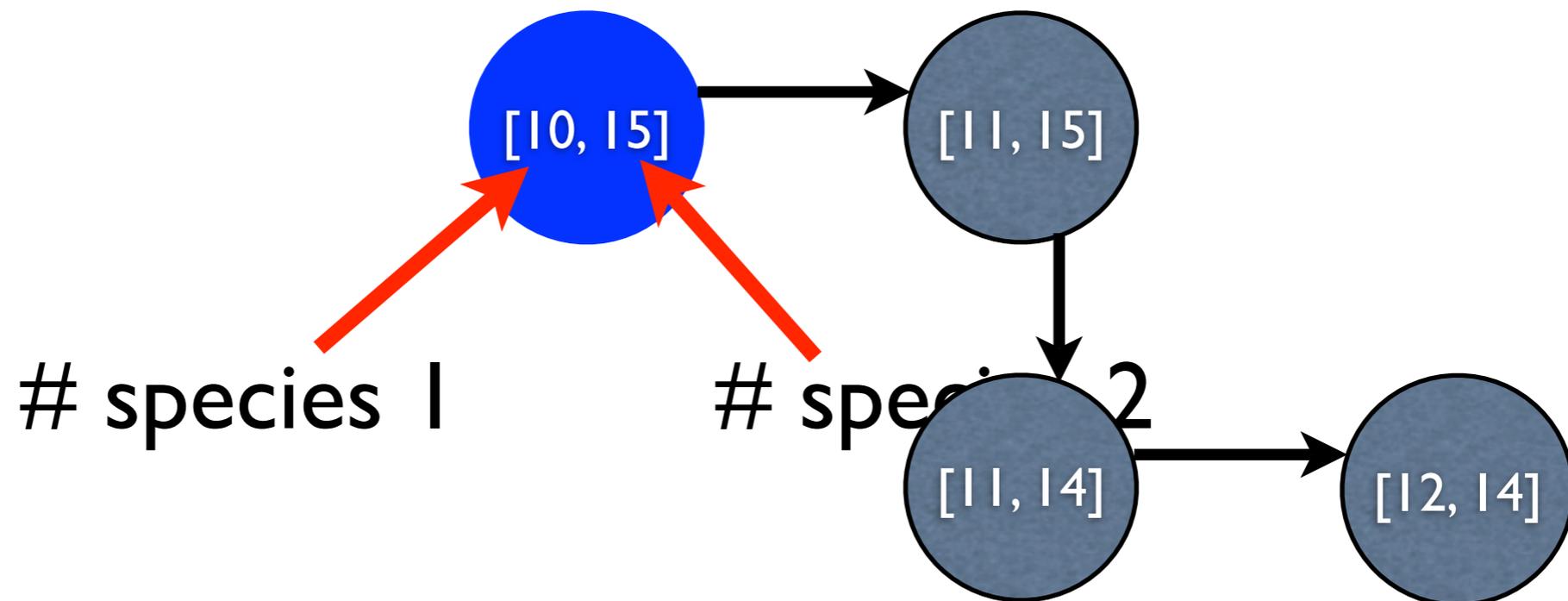
For a bimolecular reaction:  $c$  is numerically equal to  $k/\Omega$ , where  $k$  is the reaction rate constant of conventional deterministic chemical kinetics

# The Markov Description of Biochemical Processes

# A Jump-Markov description of chemical kinetics

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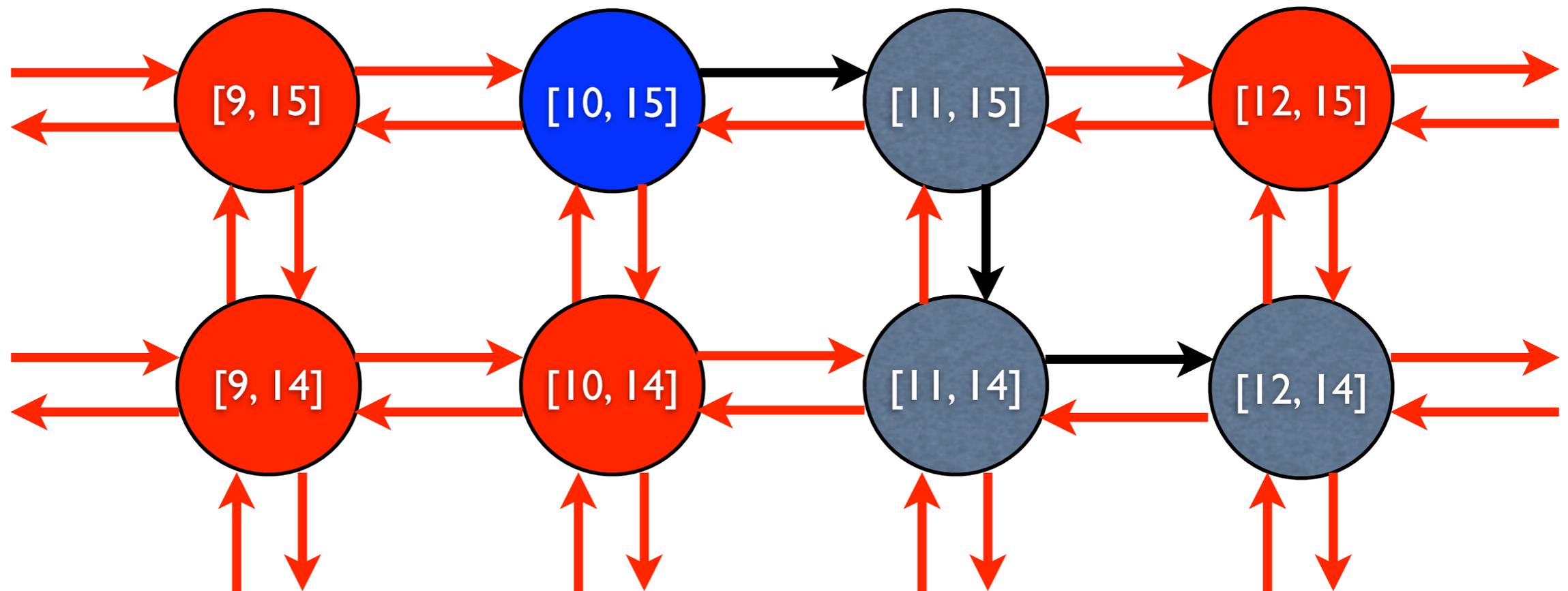
- At any time, the state of the system is *defined* by its integer population vector:  $\mathbf{x} \in \mathbb{Z}^N$
- Reactions are transitions from one state to another:



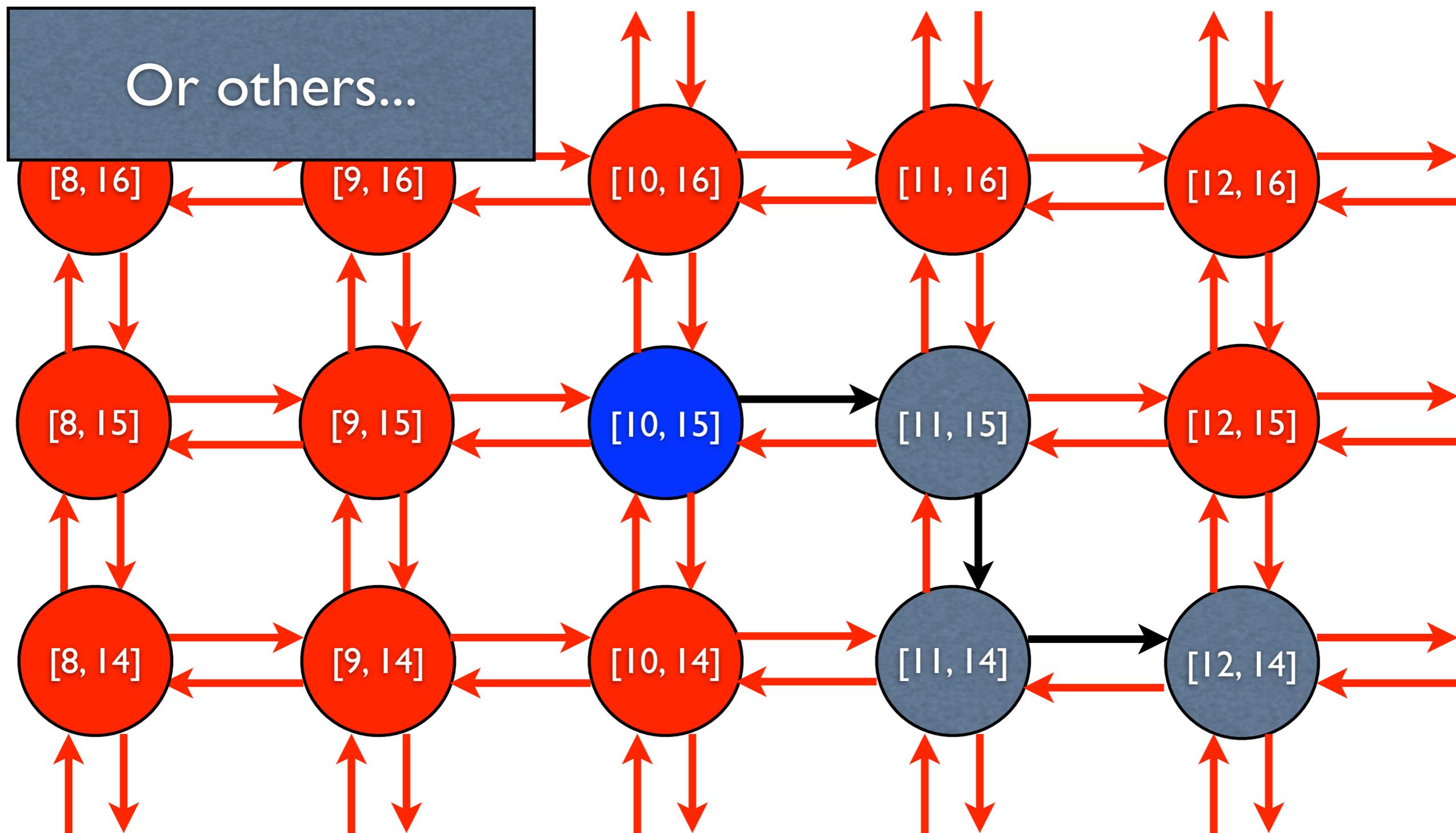
# A Jump-Markov description of chemical kinetics

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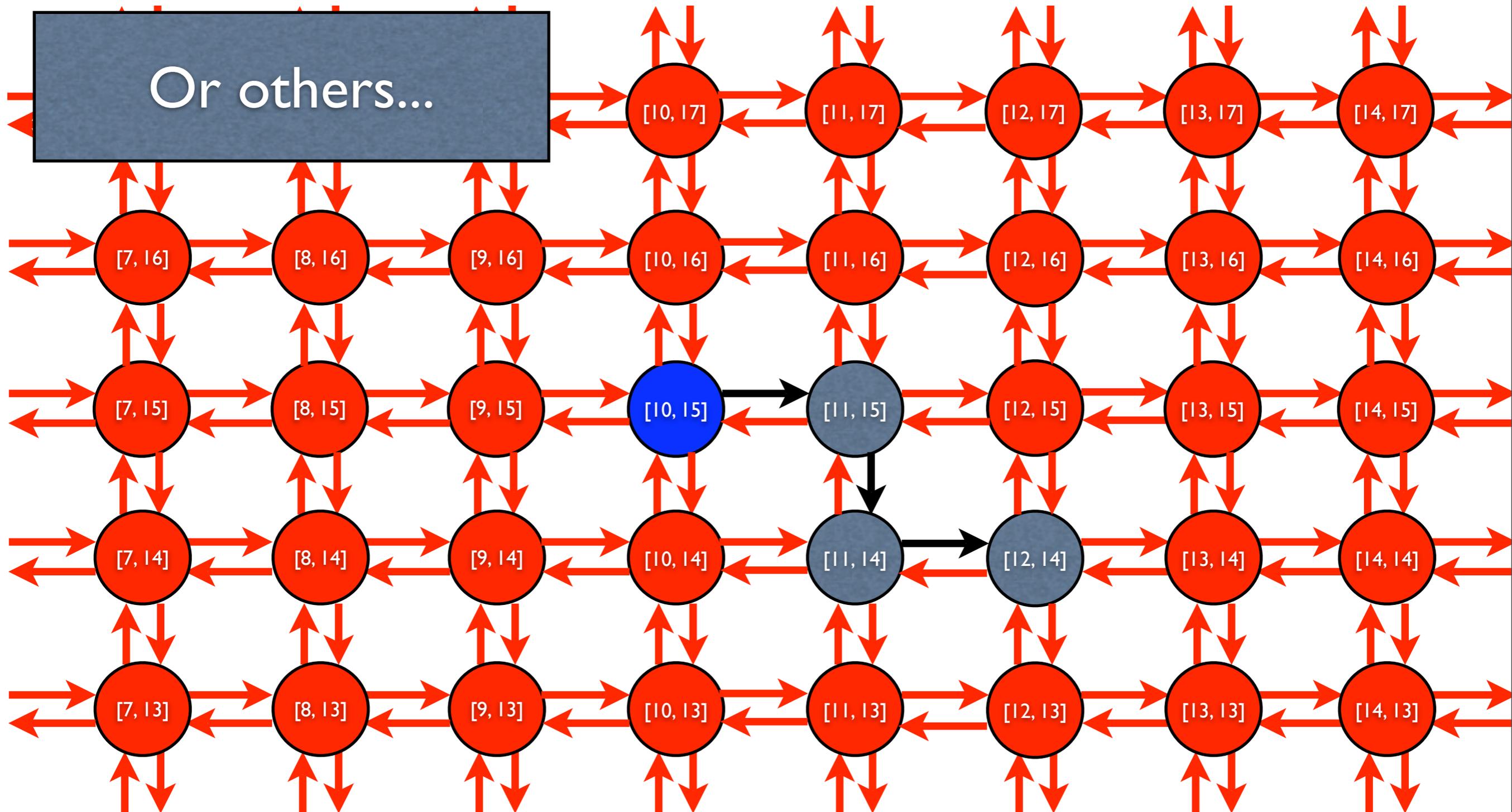
- At any time, the state of the system is *defined* by its integer population vector:  $\mathbf{x} \in \mathbb{Z}^N$
- Reactions are transitions from one state to another:
- These reactions are random, others could have occurred:



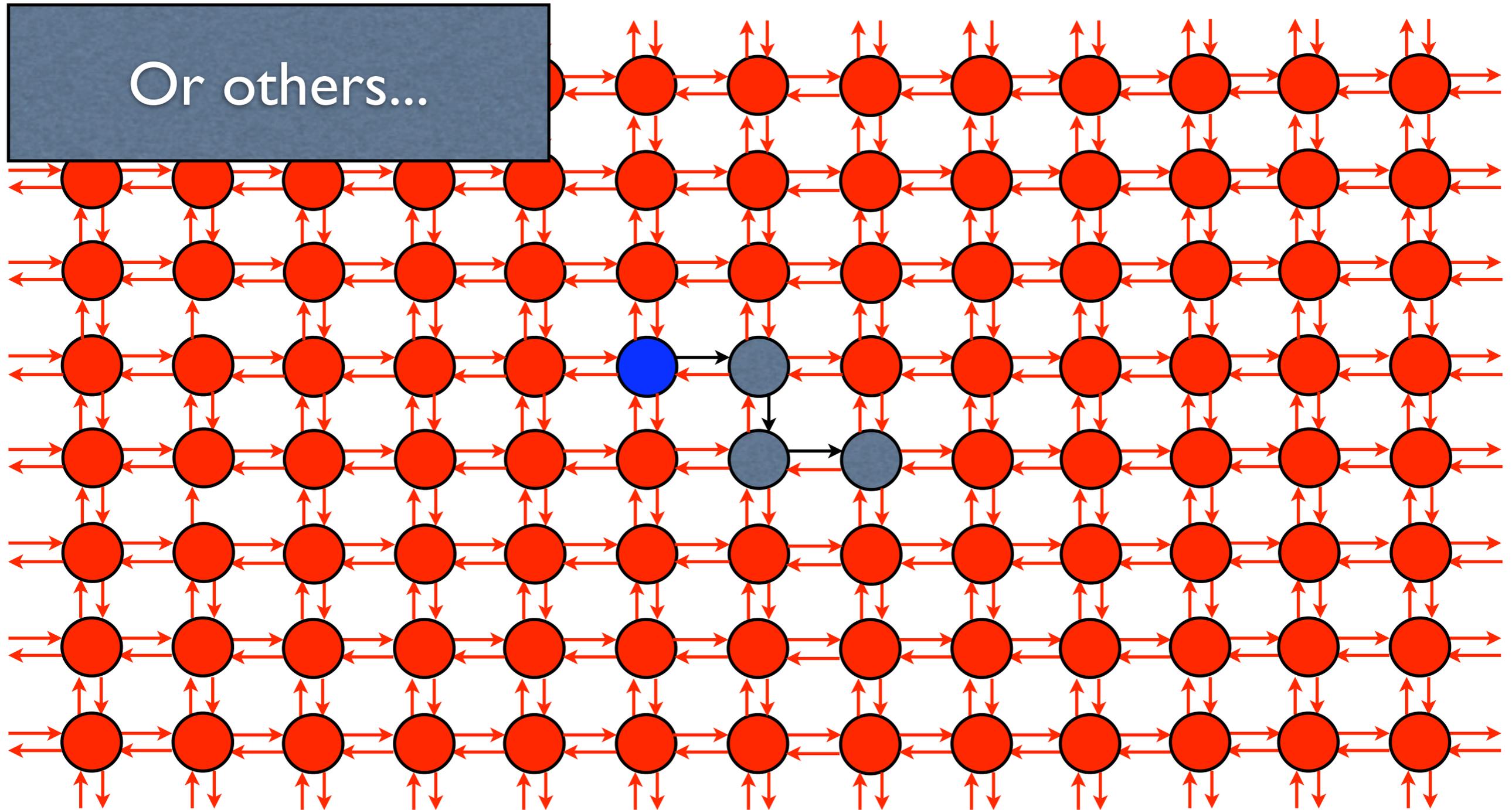
# A Jump-Markov description of chemical kinetics



# A Jump-Markov description of chemical kinetics

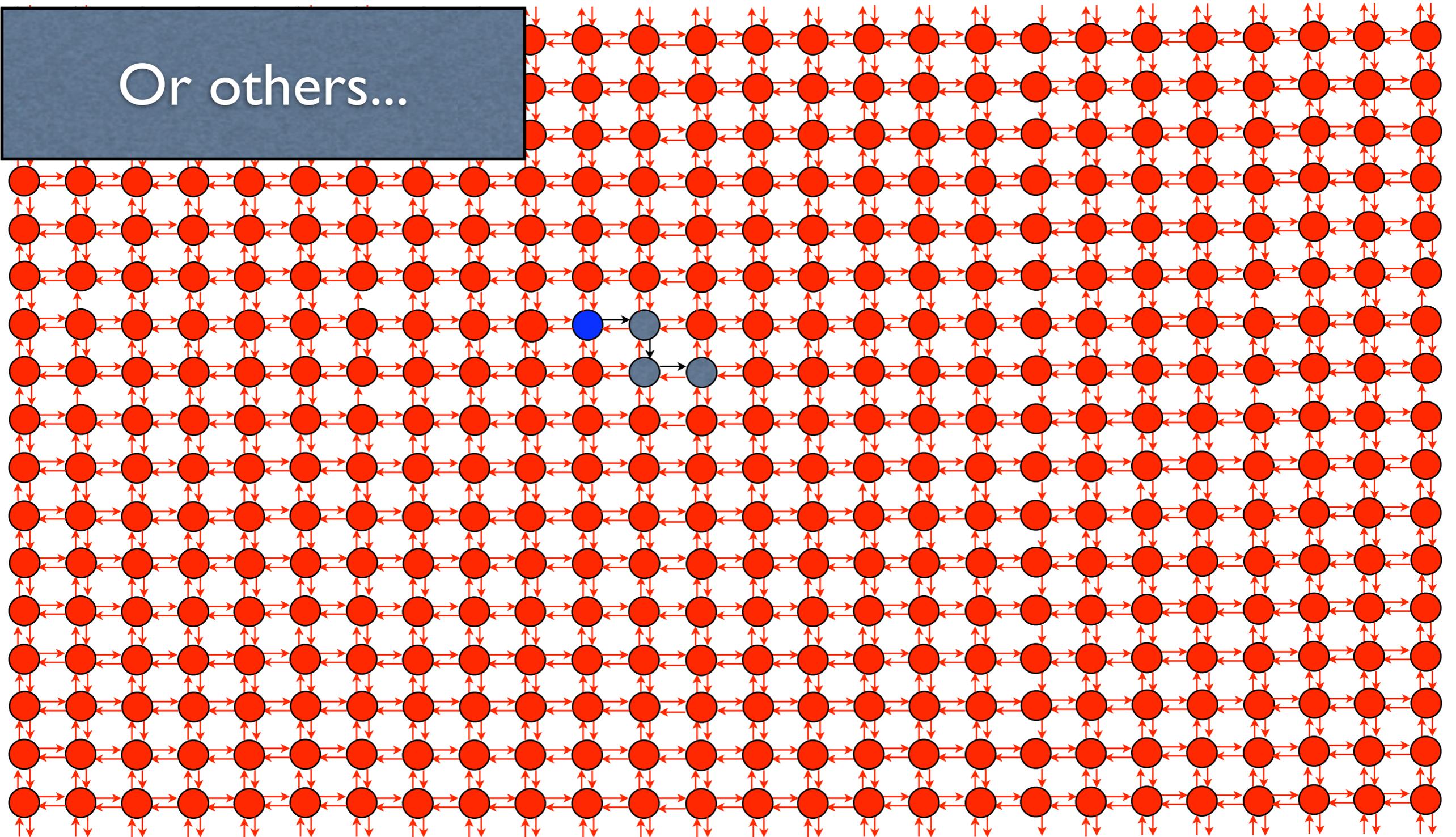


# A Jump-Markov description of chemical kinetics



# A Jump-Markov description of chemical kinetics

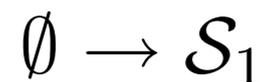
Or others...



# Reaction Stoichiometry

- The Stoichiometric vector,  $\mathbf{s}$ , refers to the relative change in the population vector after a reaction.
- There may be many different reactions for a given stoichiometry.

$$\mathbf{s}_1 = [1, 0]^T$$



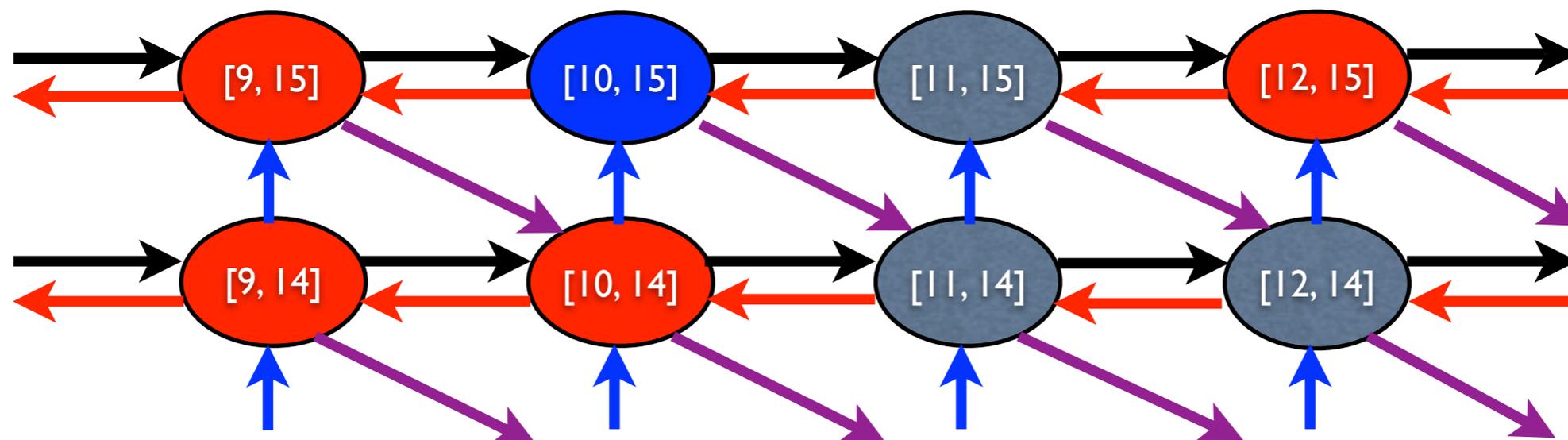
$$\mathbf{s}_2 = [-1, 0]^T$$



$$\mathbf{s}_3 = [0, 1]^T$$



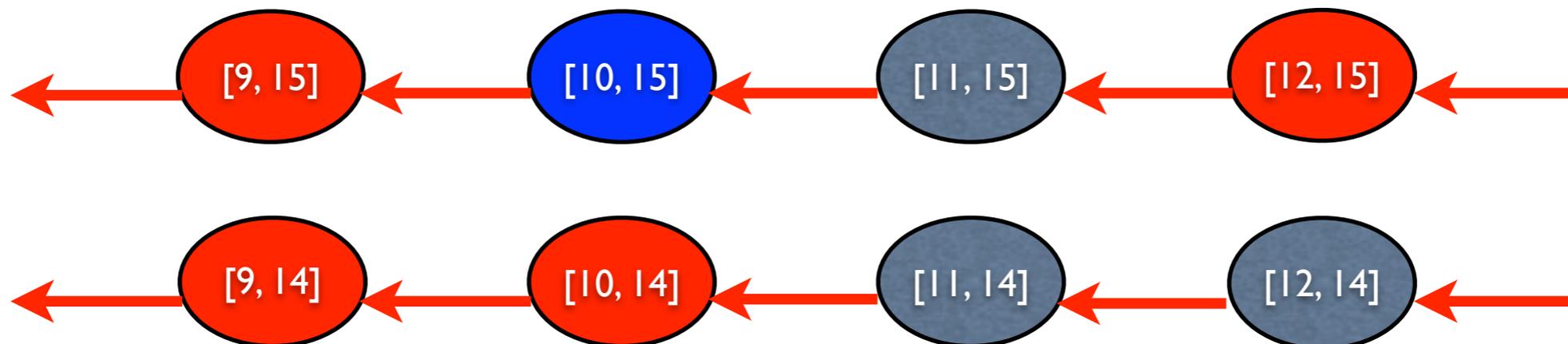
$$\mathbf{s}_4 = [1, -1]^T$$



# Reaction Propensities

- The propensity,  $w$ , of a reaction is its rate.
- $w_{\mu} dt$  is the probability that the  $\mu^{th}$  reaction will occur in a time step of length  $dt$ .
- Typically, propensities depend only upon reactant populations.

$\mathbf{s}_2 = [-1, 0]^T$	$w_2(x_1, x_2)$
$\mathcal{S}_1 + \mathcal{S}_1 \rightarrow \mathcal{S}_1$	$k_1 x_2 (x_1 - 1) / 2$
$\mathcal{S}_1 + \mathcal{S}_2 \rightarrow \mathcal{S}_2$	$k_2 x_1 x_2$
$\mathcal{S}_1 \rightarrow \emptyset$	$k_3 x_1$



Markov is a forgetful process

# Markov Reaction Times

---

Probability reaction will occur in  $[t, t + \Delta t)$ :  $w\Delta t + \mathcal{O}(\Delta t)^2$

Probability reaction *will not occur* in  $[t, t + \Delta t)$   $1 - w\Delta t + \mathcal{O}(\Delta t)^2$

Probability a reaction *will not occur* in two such time intervals  $[t, t + 2\Delta t)$ :  $(1 - w\Delta t + \mathcal{O}(\Delta t)^2)^2 = 1 - 2w\Delta t + \mathcal{O}(\Delta t)^2$

Suppose that  $\tau = K\Delta t$ , then the probability that *no reaction will occur* in the interval  $[t, t + \tau)$  is

$$\left(1 - w\frac{\tau}{K} + \mathcal{O}(K^{-2})\right)^K$$

Taking the limit as  $K$  goes to infinity yields that the probability that *no reaction will occur* in the interval  $[t, t + \tau)$  is

$$\lim_{k \rightarrow \infty} \left(1 - w\frac{\tau}{K} + \mathcal{O}(K^{-2})\right)^K = \exp(-w\tau)$$

# Markov Reaction Times

---

The probability that a reaction will occur in the interval  $[t, t + \tau)$  is  $F_T(\tau) = 1 - \exp(-w\tau)$ . This is a cumulative distribution.

The density (derivative) of the random number,  $T$ , is:

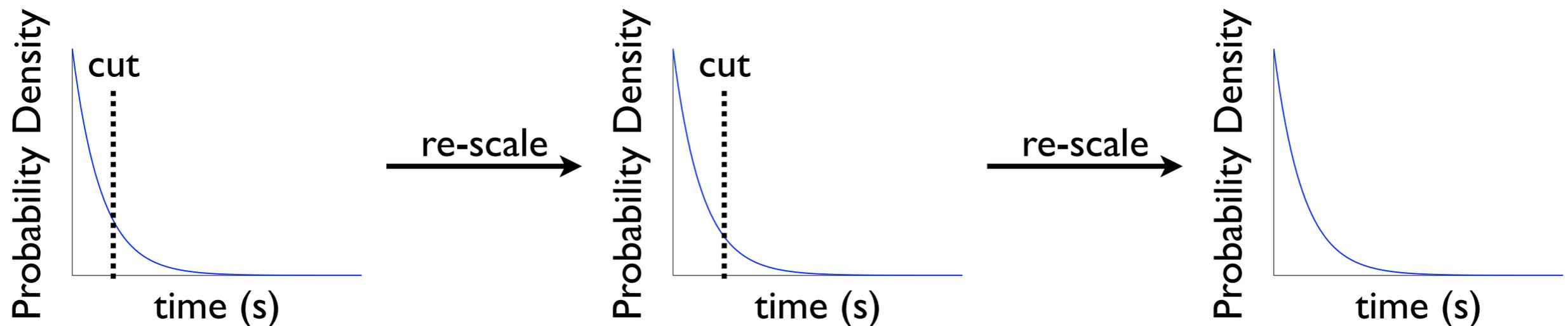
$$f_T(\tau) = \frac{1}{w} \exp(-w\tau)$$

Such a random number is known as an *exponentially* distributed random number.

Notation:  $T \in \text{EXP}(\lambda) \rightarrow T$  is an exponentially distributed r.v. with parameter:  $\lambda$ .

# Markov Reaction Times

- We have assumed that the system is fully described by the population vectors.
- If no reaction occurs, then nothing will have changed.
- Waiting times must be *memoryless* random variables.



- No matter where we cut and scale the distribution, it must always look the same.

The exponential is the *only* continuous r.v. with this property.

# Generating Reaction Times

- To generate an exponentially distributed random number, all we need is a uniform random number generator.

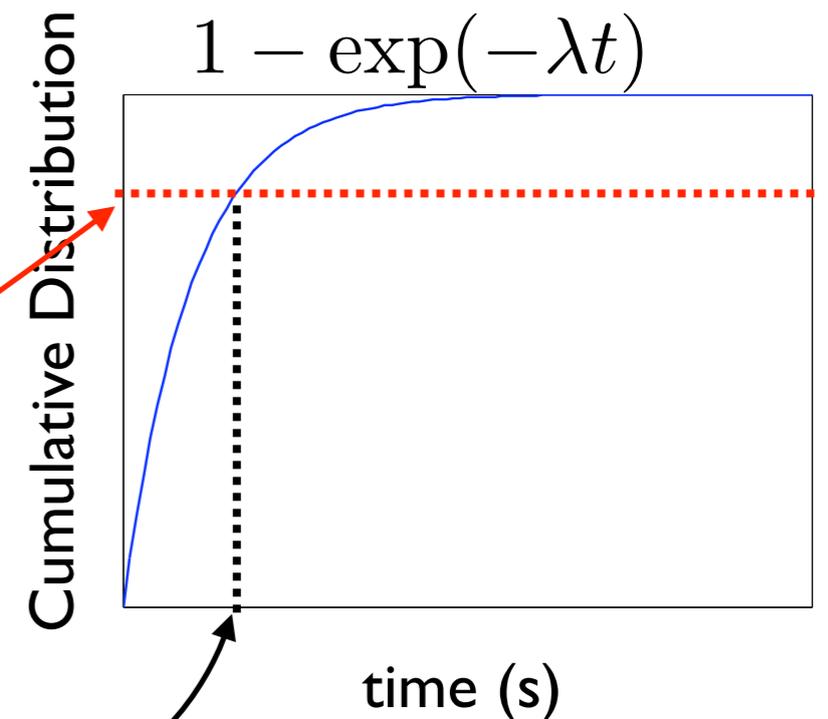
- Find the cumulative distribution,  
$$F(t) = 1 - \exp(-\lambda t)$$

- Generate uniform random number,  
$$r \in U[0, 1]$$

- Find intersection where  $F(t) = r$ :

$$\tau = \frac{1}{\lambda} \log \frac{1}{1-r}$$

- This is the time of the next reaction.



# The (Chemical) Master Equation (Forward Kolmogorov Equation)

# The Chemical Master Equation

Prob. that no reactions fire in  $[t, t + dt] = 1 - \sum_k w_k(x)dt + \mathcal{O}(dt^2)$

Prob. that reaction  $R_k$  fires once in  $[t, t + dt] = w_k(x)dt + \mathcal{O}(dt^2)$

Prob. that more than one reaction fires in  $[t, t + dt] = \mathcal{O}(dt^2)$

$$\begin{aligned}
 p(x, t + dt) = & \text{at } x \quad \text{No reaction fires} \\
 & p(x, t) \left( 1 - \sum_k w_k(x)dt + \mathcal{O}(dt^2) \right) \\
 & + \sum_k \text{at } x - s_k \quad \text{R}_k \text{ reaction away from } x \quad \left( \sum_k w_k(x)dt + \mathcal{O}(dt^2) \right) \quad \text{R}_k \text{ fires once} \\
 & + \mathcal{O}(dt^2) \quad \text{more than one reaction in } dt
 \end{aligned}$$

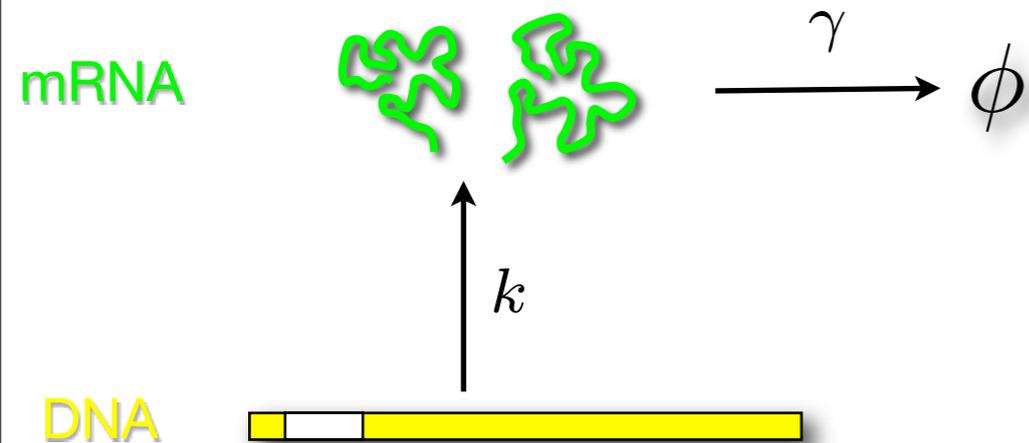
$$p(x, t + dt) - p(x, t) = -p(x, t) \sum_k w_k(x)dt + \sum_k p(x - s_k, t)w_k(x)dt + \mathcal{O}(dt^2)$$

## The Chemical Master Equation

$$\frac{dp(x, t)}{dt} = -p(x, t) \sum_k w_k(x) + \sum_k p(x - s_k, t)w_k(x - s_k)$$

Example: Transcription and degradation of mRNA  
(as a birth-death process)

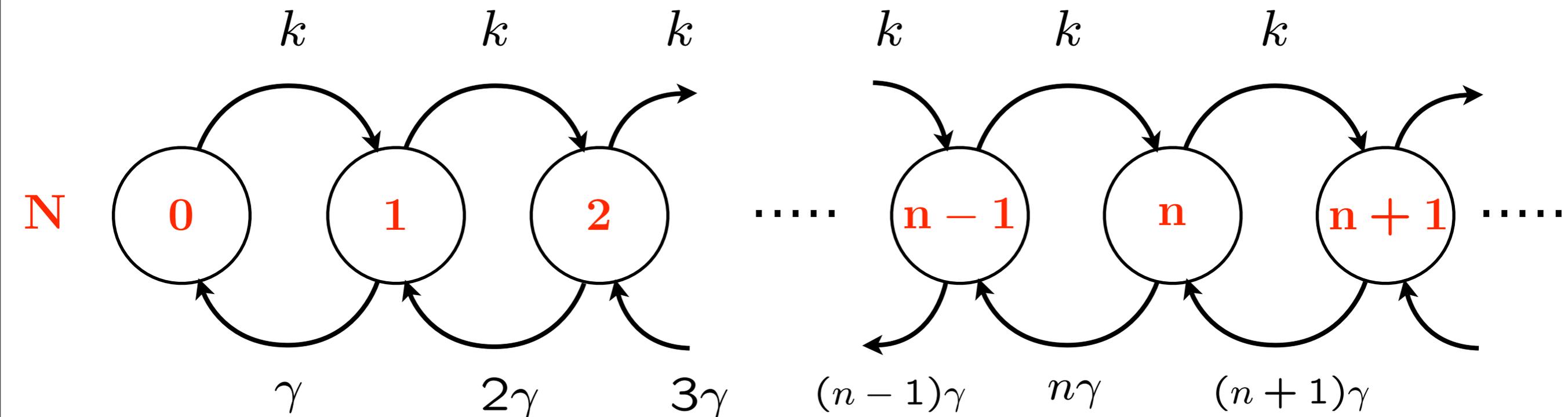
# RNA Copy Number as a Random Variable



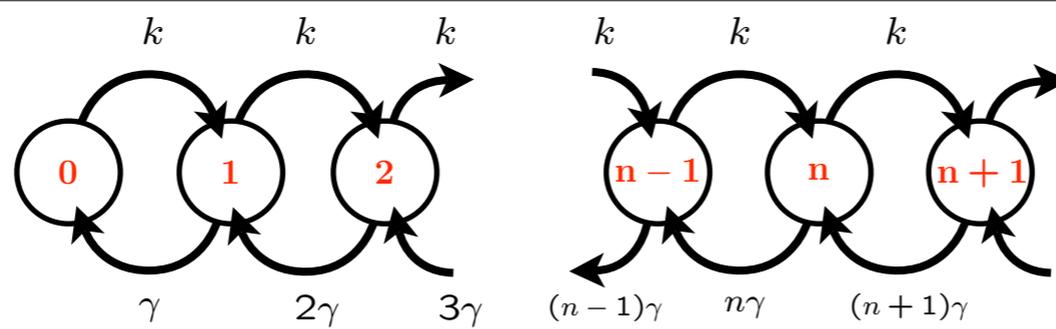
mRNA copy number  $N(t)$  is a **random variable**

**Transcription:** Probability a single mRNA is **transcribed** in time  $dt$  is  $k dt$

**Degradation:** Probability a single mRNA is **degraded** in time  $dt$  is  $n\gamma dt$



## Key Question:



Find  $p(n, t)$ , the probability that  $N(t) = n$ .

$$P(n, t + dt) = P(n - 1, t) \cdot kdt$$

Prob.  $\{N(t) = n - 1 \text{ and mRNA created in } [t, t+dt)\}$

$$+ P(n + 1, t) \cdot (n + 1)\gamma dt$$

Prob.  $\{N(t) = n + 1 \text{ and mRNA degraded in } [t, t+dt)\}$

$$+ P(n, t) \cdot (1 - kdt)(1 - n\gamma dt)$$

Prob.  $\{N(t) = n \text{ and}$

mRNA not created nor degraded in  $[t, t+dt)\}$

$$P(n, t + dt) - P(n, t) = P(n - 1, t)kdt + P(n + 1, t)(n + 1)\gamma dt - P(n, t)(k + n\gamma)dt + O(dt^2)$$

Dividing by  $dt$  and taking the limit as  $dt \rightarrow 0$

### The Chemical Master Equation

$$\frac{d}{dt}P(n, t) = kP(n - 1, t) + (n + 1)\gamma P(n + 1, t) - (k + n\gamma)P(n, t)$$

# mRNA Stationary Distribution

---

We look for the stationary distribution  $P(n, t) = p(n) \forall t$

The stationary solution satisfies:  $\frac{d}{dt}P(n, t) = 0$

From the Master Equation ...

$$(k + n\gamma)p(n) = kp(n - 1) + (n + 1)\gamma p(n + 1)$$

$$n = 0 \quad kp(0) = \gamma p(1)$$

$$n = 1 \quad kp(1) = 2\gamma p(2)$$

$$n = 2 \quad kp(2) = 3\gamma p(3)$$

⋮

$$kp(n - 1) = n\gamma p(n)$$

$kp(n-1) = n\gamma p(n)$  We can express  $p(n)$  as a function of  $p(0)$ :

$$\begin{aligned} p(n) &= \frac{k}{\gamma} \frac{1}{n} p(n-1) \\ &= \left(\frac{k}{\gamma}\right)^2 \frac{1}{n} \frac{1}{n-1} p(n-2) \\ &\vdots \\ &= \left(\frac{k}{\gamma}\right)^n \frac{1}{n!} p(0) \end{aligned}$$

We can solve for  $p(0)$  using the fact  $\sum_{n=0}^{\infty} p(n) = 1$

$$\begin{aligned} 1 &= \sum_{n=0}^{\infty} \left(\frac{k}{\gamma}\right)^n \frac{1}{n!} p(0) \\ &= e^{k/\gamma} p(0) \quad \Rightarrow \quad p(0) = e^{-k/\gamma} \end{aligned}$$

$$p(n) = e^{-a} \frac{a^n}{n!} \quad a = \frac{k}{\gamma}$$

**Poisson Distribution**

We can compute the mean and variance of the Poisson RV  $\bar{N}$  with density  $p(n) = e^{-a} \frac{a^n}{n!}$ :

$$\mu = E[\bar{N}] = \sum_{n=0}^{\infty} np(n) = e^{-a} \sum_{n=0}^{\infty} n \frac{a^n}{n!} = a$$

The second moment

$$E[\bar{N}^2] = \sum_{n=0}^{\infty} n^2 p(n) = a^2 + a$$

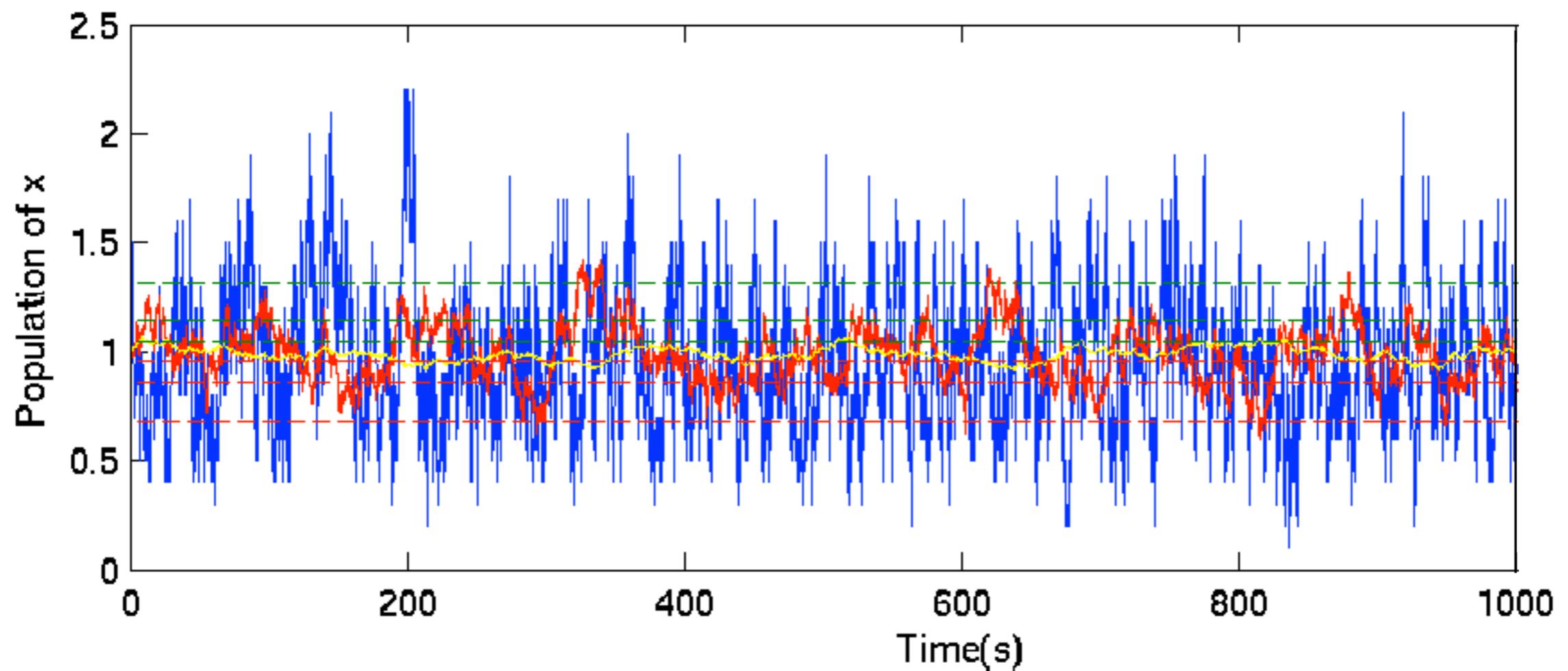
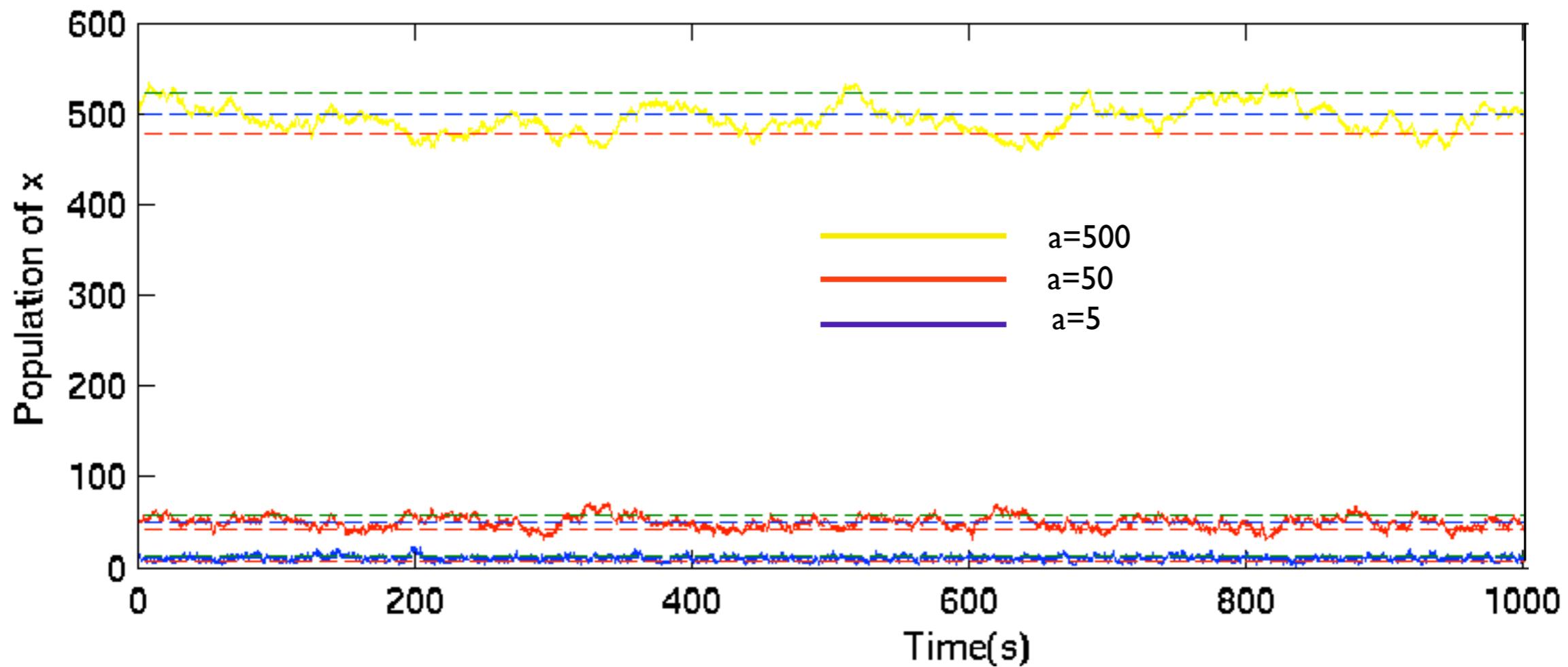
Therefore,

$$\sigma^2 = E[\bar{N}^2] - E[\bar{N}]^2 = a$$

$$\text{mean} = \text{variance} = a$$

The coefficient of variation  $C_v = \sigma/\mu$  is

$$C_v = \frac{1}{\sqrt{a}} = \frac{1}{\sqrt{\mu}}$$



# The Relationship of Deterministic to Stochastic Biochemical Processes.

# Relationship of Stochastic ( $X$ ) and Deterministic ( $\Phi$ ) Descriptions

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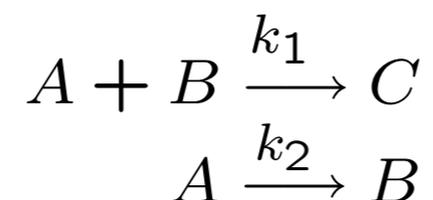
Given  $N$  species  $X_1, \dots, X_N$  and  $M$  elementary reactions. Let  $\Phi_i := [X_i]$ .

A deterministic description can be obtained from mass-action kinetics:

$$\frac{d\Phi}{dt} = Sf(\Phi)$$

where  $f(\cdot)$  is at most a second order monomial. It depends on the type of reactions and their rates.

**Example:**



$$\begin{aligned} \frac{d\Phi_A}{dt} &= -k_1\Phi_A\Phi_B - k_2\Phi_A \\ \frac{d\Phi_B}{dt} &= -k_1\Phi_A\Phi_B + k_2\Phi_A \\ \frac{d\Phi_C}{dt} &= k_1\Phi_A\Phi_B \end{aligned}$$

or

$$\frac{d\Phi}{dt} = Sf(\Phi) \text{ where } S = \begin{bmatrix} -1 & -1 \\ -1 & 1 \\ 1 & 0 \end{bmatrix}, f(\Phi) = \begin{bmatrix} k_1\Phi_A\Phi_B \\ k_2\Phi_A \end{bmatrix}$$

# Relationship of Stochastic ( $X$ ) and Deterministic ( $\Phi$ ) Descriptions

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Define  $X^\Omega(t) = \frac{X(t)}{\Omega}$ .

Question: How does  $X^\Omega(t)$  relate to  $\Phi(t)$ ?

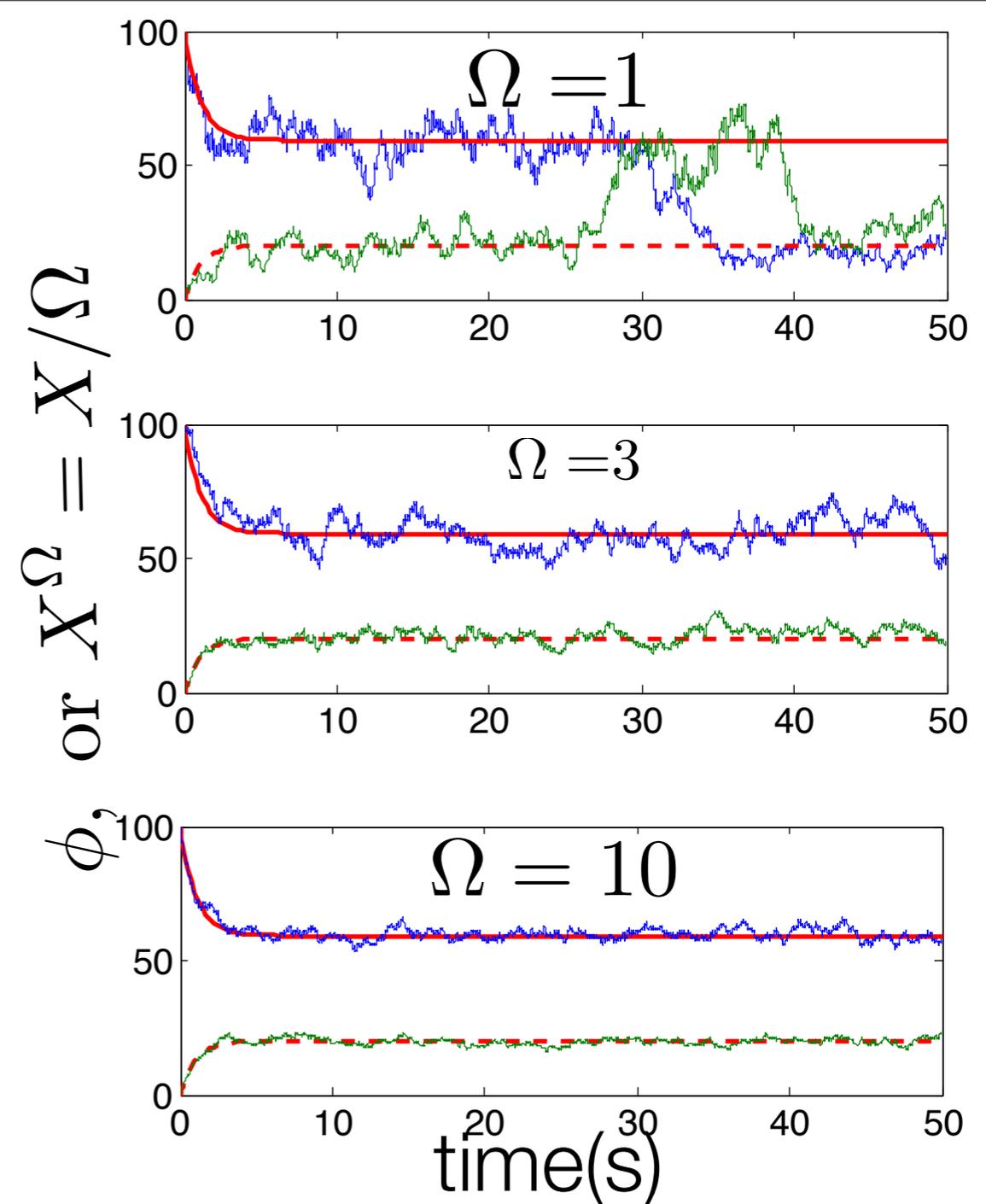
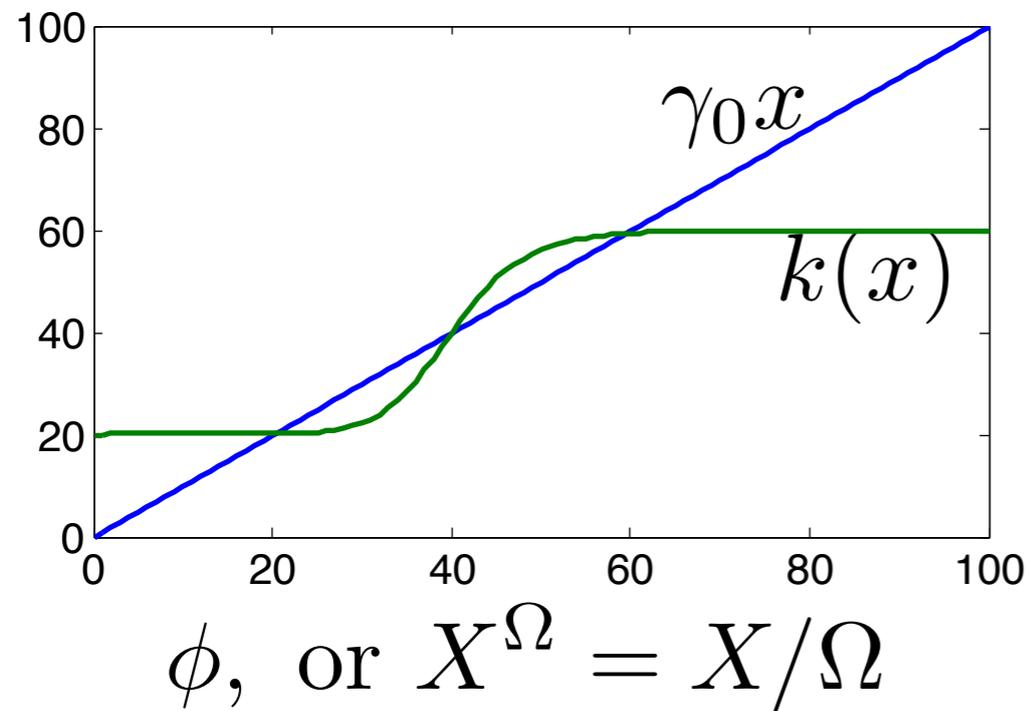
**Fact:** Let  $\Phi(t)$  be the **deterministic** solution to the reaction rate equations

$$\frac{d\Phi}{dt} = Sf(\Phi), \quad \Phi(0) = \Phi_0.$$

Let  $X^\Omega(t)$  be the **stochastic** representation of the same chemical systems with  $X^\Omega(0) = \Phi_0$ . Then for every  $t \geq 0$ :

$$\lim_{\Omega \rightarrow \infty} \sup_{s \leq t} |X^\Omega(s) - \Phi(s)| = 0 \text{ a.s.}$$

$x$  produced with rate  $k(x)$   
and degraded with rate  $\gamma_0 x$ .



$$w_1(\phi) = \gamma_0 \phi$$

$$w_2(\phi) = \left( 20 + 40 \frac{\phi^{10}}{40^{10} + \phi^{10}} \right)$$

Deterministic

$$w_1(X) = \Omega \gamma_0 X / \Omega = \gamma_0 X$$

$$w_2(X) = \Omega \left( 20 + 40 \frac{(X/\Omega)^{10}}{40^{10} + (X/\Omega)^{10}} \right)$$

Stochastic

# Moment Computations

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- Affine Propensity
- Moment Closures

# Moment Computations

---

For the first moment  $E[X_i]$ , multiply the CME by  $x_i$  and sum over all  $(x_1, \dots, x_N) \in \mathbb{N}^N$

For the second moment  $E[X_i X_j]$ , multiply the CME by  $x_i x_j$  and sum over all  $(x_1, \dots, x_N) \in \mathbb{N}^N$

$$\frac{dE[X_i]}{dt} = \sum_{k=1}^M s_{ik} E[w_k(X)]$$

$$\frac{dE[X_i X_j]}{dt} = \sum_{k=1}^M (s_{ik} E[X_j w_k(X)] + E[X_i w_k(X)] s_{jk} + s_{ik} s_{jk} E[w_k(X)])$$

Let  $w(x) = [w_1(x), \dots, w_M(x)]^T$

In matrix notation:

$$\begin{aligned} \frac{dE[X]}{dt} &= S E[w(X)] \\ \frac{dE[XX^T]}{dt} &= S E[w(X)X^T] + E[w(X)X^T]^T S^T + S \{diag E[w(X)]\} S^T \end{aligned}$$

# Affine Propensity

---

Suppose the propensity function is affine:

$$w(x) = Wx + w_0, \quad (W \text{ is } N \times N, w_0 \text{ is } N \times 1)$$

Then  $E[w(X)] = WE[X] + w_0$ , and  $E[w(X)X^T] = WE[XX^T] + w_0E[X^T]$ .

This gives us the moment equations:

$\frac{d}{dt}E[X] = SWE[X] + Sw_0$	First Moment
$\begin{aligned} \frac{d}{dt}E[XX^T] &= SWE[XX^T] + E[XX^T]W^T S^T + S \text{diag}(WE[X] + w_0)S^T \\ &+ Sw_0E[X^T] + E[X]w_0^T S^T \end{aligned}$	Second Moment

These are linear ordinary differential equations and can be easily solved!

# Affine Propensity (cont.)

---

Define the covariance matrix  $\Sigma = E[(X - E[X])(X - E[X])^T]$ .

We can also compute covariance equations:

$$\frac{d}{dt}\Sigma = SW\Sigma + \Sigma W^T S^T + S \text{diag}(WE[X] + w_0)S^T$$

## Steady-state Case

The steady-state moments and covariances can be obtained by solving linear algebraic equations:

Let  $\bar{X} = \lim_{t \rightarrow \infty} E[X(t)]$  and  $\bar{\Sigma} = \lim_{t \rightarrow \infty} \Sigma(t)$ .

Then

$$SW\bar{X} = -Sw_0$$

$$SW\bar{\Sigma} + \bar{\Sigma}W^T S^T + S \text{diag}(W\bar{X} + w_0)S^T = 0$$

# Fluctuations Arise from Noise Driven Dynamics

---

Define  $A = SW$ , and  $B = S\sqrt{\text{diag}(W\bar{X} + w_0)}$ .

The steady-state covariances equation

$$SW\bar{\Sigma} + \bar{\Sigma}W^T S^T + S \text{diag}(W\bar{X} + w_0)S^T = 0$$

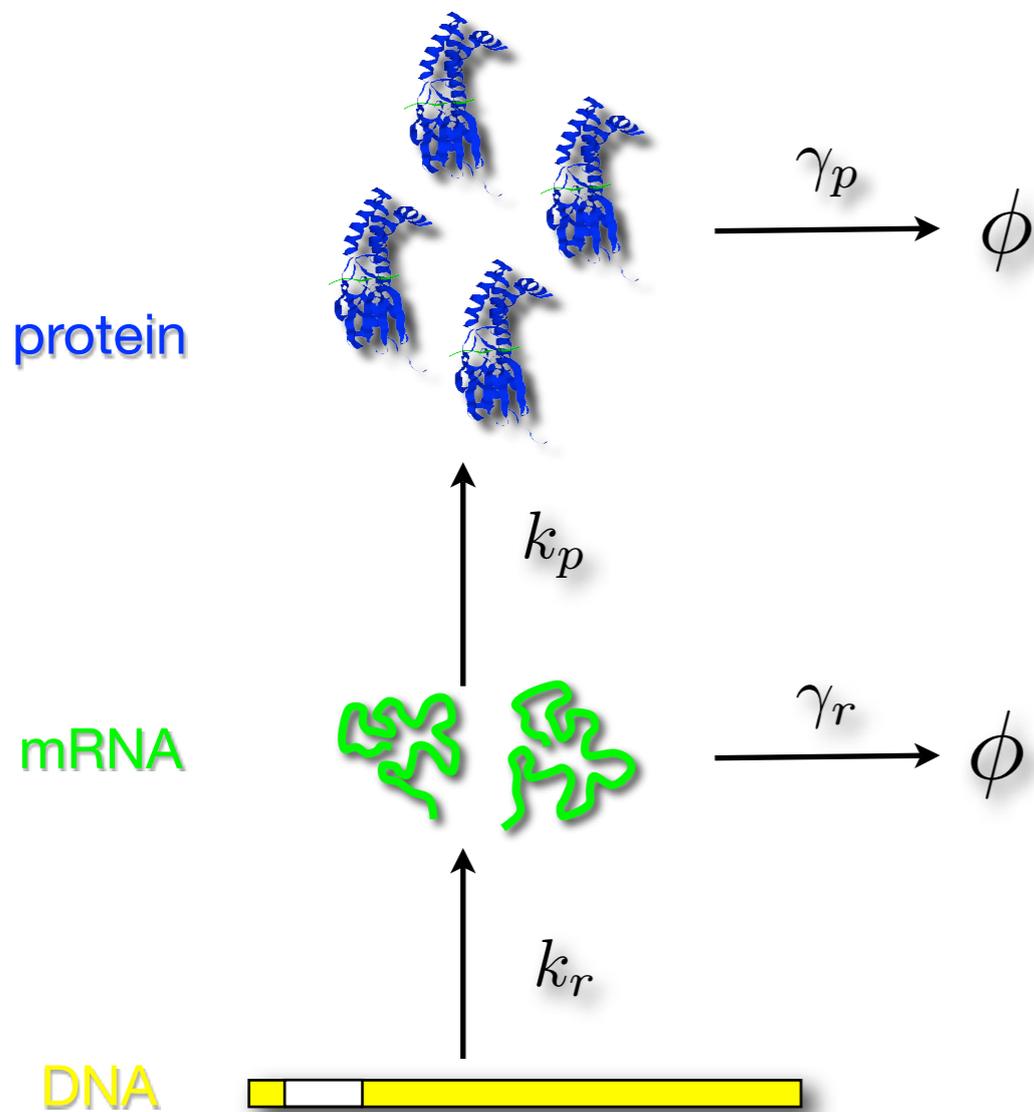
becomes

$$A\bar{\Sigma} + \bar{\Sigma}A^T + BB^T = 0 \quad \text{Lyapunov Equation}$$

# Example: Gene Expression

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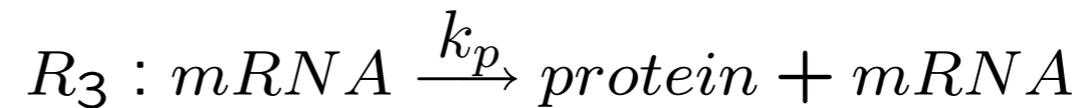
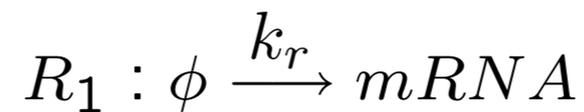
# Application to Gene Expression



## Reactants

$X_1(t)$  is # of mRNA;  $X_2(t)$  is # of protein

## Reactions



## Stoichiometry and Propensity

$$S = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

$$w(X) = \begin{bmatrix} k_r \\ \gamma_r X_1 \\ k_p X_1 \\ \gamma_p X_2 \end{bmatrix} = \underbrace{\begin{bmatrix} 0 & 0 \\ \gamma_r & 0 \\ k_p & 0 \\ 0 & \gamma_p \end{bmatrix}}_W \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} + \underbrace{\begin{bmatrix} k_r \\ 0 \\ 0 \\ 0 \end{bmatrix}}_{w_0}$$

## Steady-State Moments

$$A = SW = \begin{bmatrix} -\gamma_r & 0 \\ k_p & -\gamma_p \end{bmatrix}, \quad Sw_0 = \begin{bmatrix} k_r \\ 0 \end{bmatrix}$$

$$\bar{X} = -A^{-1}Sw_0 = \begin{bmatrix} \frac{k_r}{\gamma_r} \\ \frac{k_p k_r}{\gamma_p \gamma_r} \end{bmatrix}$$

## Steady-State Covariance

$$BB^T = S \operatorname{diag}(W\bar{X} + w_0)S^T = \begin{bmatrix} 2k_r & 0 \\ 0 & \frac{2k_p k_r}{\gamma_r} \end{bmatrix}$$

The steady-state covariances equation

$$A\bar{\Sigma} + \bar{\Sigma}A^T + BB^T = 0 \quad \text{Lyapunov Equation}$$

can be solved algebraically for  $\bar{\Sigma}$ .

$$\bar{\Sigma} = \begin{bmatrix} \frac{k_r}{\gamma_r} & \frac{k_p k_r}{\gamma_r(\gamma_r + \gamma_p)} \\ \frac{k_p k_r}{\gamma_r(\gamma_r + \gamma_p)} & \frac{k_p k_r}{\gamma_p \gamma_r} \left(1 + \frac{k_p}{\gamma_r + \gamma_p}\right) \end{bmatrix}$$

## Coefficients of Variation

$$C_{vr}^2 = \frac{1}{\frac{k_r}{\gamma_r}} = \frac{1}{\bar{X}_1}$$

$$C_{vp}^2 = \frac{1}{\frac{k_r k_p}{\gamma_r \gamma_p}} \left( 1 + \frac{k_p}{\gamma_r + \gamma_p} \right) = \frac{1}{\bar{X}_2} \left( 1 + \frac{k_p}{\gamma_r + \gamma_p} \right)$$

**Question:** Does a large  $\bar{X}_2$  imply a small  $C_{vp}$ ?

$$\begin{aligned} C_{vp}^2 &= \frac{1}{\frac{k_r k_p}{\gamma_r \gamma_p}} \left( 1 + \frac{k_p}{\gamma_r + \gamma_p} \right) \\ &\geq \frac{1}{\frac{k_r k_p}{\gamma_r \gamma_p}} \left( \frac{k_p}{\gamma_r + \gamma_p} \right) = \frac{\gamma_r \gamma_p}{k_r} \cdot \frac{1}{\gamma_r + \gamma_p} \end{aligned}$$

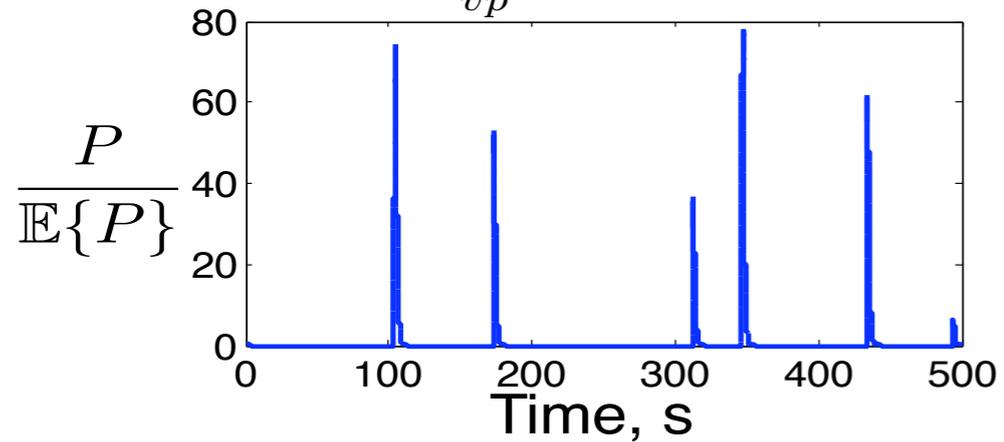
$\bar{X}_2 = \frac{k_r k_p}{\gamma_r \gamma_p}$ , which can be chosen *independently* from  $C_{vp}$ .

**Large mean does not imply small fluctuations!**

$$\mathbb{E}\{P\} = 100, \quad \gamma_r = \gamma_p = 1$$

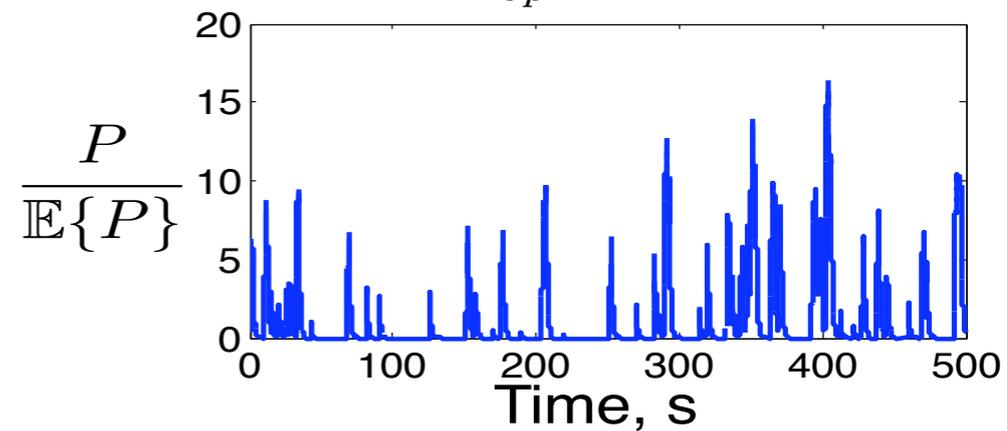
$$k_r = 0.01 \quad k_p = 10,000$$

$$C_{vp}^2 = 50.01$$



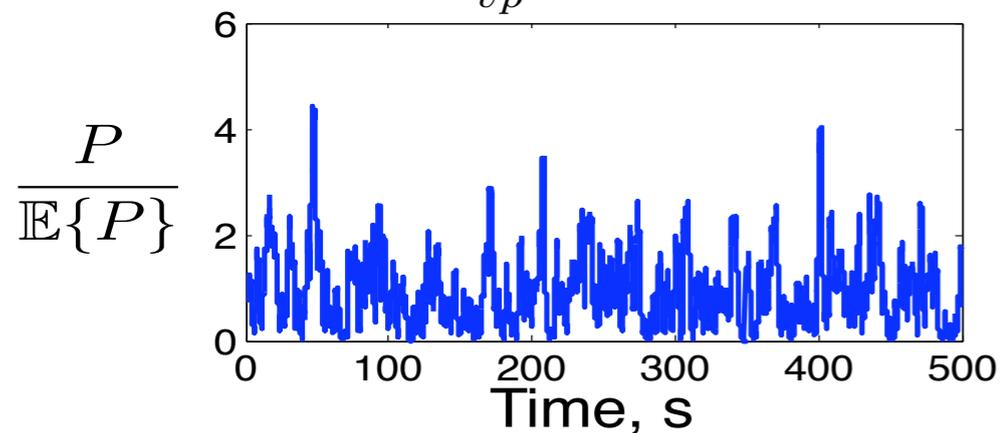
$$k_r = 0.1 \quad k_p = 1000$$

$$C_{vp}^2 = 5.01$$



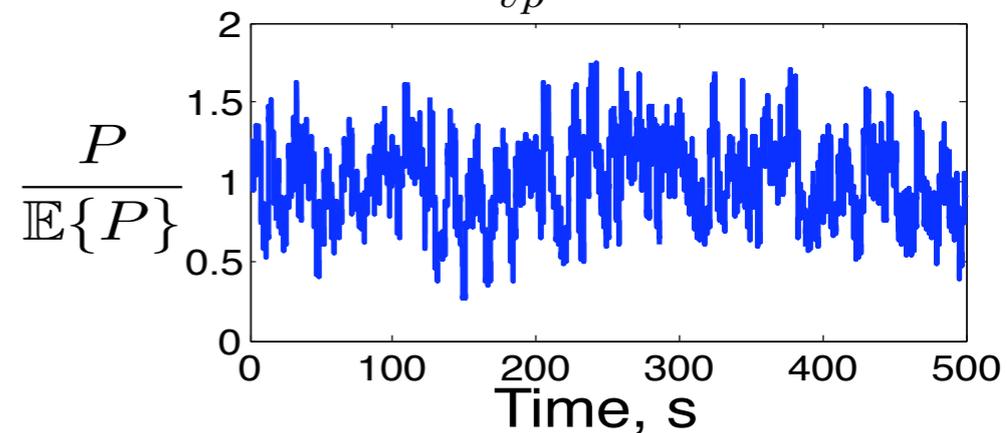
$$k_r = 1 \quad k_p = 100$$

$$C_{vp}^2 = 0.51$$



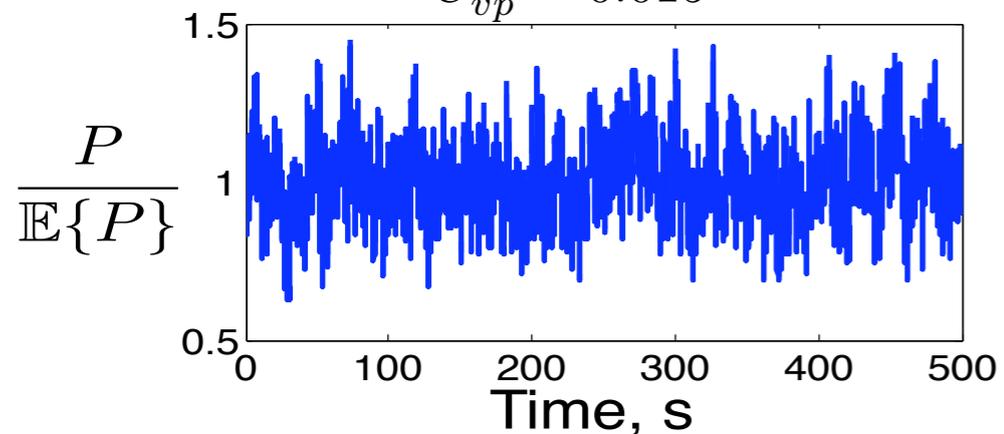
$$k_r = 10 \quad k_p = 10$$

$$C_{vp}^2 = 0.06$$



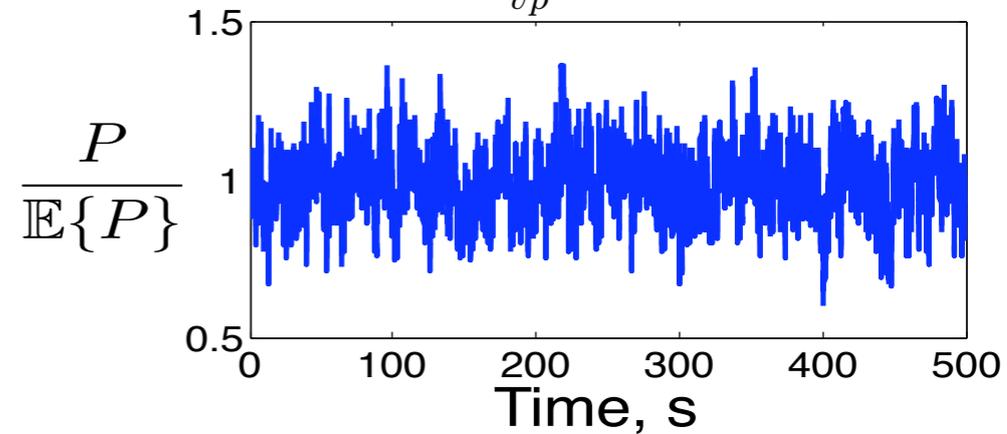
$$k_r = 100 \quad k_p = 1$$

$$C_{vp}^2 = 0.015$$



$$k_r = 1000 \quad k_p = 0.1$$

$$C_{vp}^2 = 0.0105$$



# Moment Computations

---

- Affine Propensity
- **Moment Closures**

# Moment Closures.

---

From before, the mean level changes as:

$$\frac{dE[X]}{dt} = SE[w(X)]$$

- When Second and Higher order terms exist in the propensity functions, each moment depends upon higher moments.

▶ For example, if  $w(X) = \mathbf{u}X^T X \mathbf{v}$ , then

$$\frac{dE[X]}{dt} = S\mathbf{u}E[X^T X]\mathbf{v}$$

- The first moment depends upon the second; the second upon the third; and so on.
- Moment closures are approximations that attempt to remove this dependence.

# Moment Closures.

---

$$\frac{dE[X_i]}{dt} = \sum_{k=1}^M s_{ik} E[w_k(X)]$$

$$\frac{dE[X_i X_j]}{dt} = \sum_{k=1}^M (s_{ik} E[X_j w_k(X)] + E[X_i w_k(X)] s_{jk} + s_{ik} s_{jk} E[w_k(X)])$$

$$\frac{d}{dt} \begin{bmatrix} \{\mu_i\} \\ \{\sigma_{ij}\} \end{bmatrix} = \begin{bmatrix} f_1(\{\mu_i\}, \{\sigma_{ij}\}) + u_1(\{\mu_i\}, \{\sigma_{ij}\}, \{\sigma_{ijk}\}, \dots) \\ f_2(\{\mu_i\}, \{\sigma_{ij}\}) + u_2(\{\mu_i\}, \{\sigma_{ij}\}, \{\sigma_{ijk}\}, \dots) \end{bmatrix},$$

$$\frac{d}{dt} \begin{bmatrix} \{\mu_i\} \\ \{\sigma_{ij}\} \end{bmatrix} = \begin{bmatrix} f_1(\{\mu_i\}, \{\sigma_{ij}\}) + \hat{u}_1(\{\mu_i\}, \{\sigma_{ij}\}) \\ f_2(\{\mu_i\}, \{\sigma_{ij}\}) + \hat{u}_2(\{\mu_i\}, \{\sigma_{ij}\}) \end{bmatrix},$$

where the choice of  $\hat{u}_1$  and  $\hat{u}_2$   
depends upon the chosen moment closure.

# Gaussian Moment Closure

---

- If one assumes that the distributions are Gaussian, then the closure is simple:

$$\sigma_{ijk} = \mathbb{E}\{(X_i - \mathbb{E}\{X_i\})(X_j - \mathbb{E}\{X_j\})(X_k - \mathbb{E}\{X_k\})\} = 0$$

- which yields:

$$\begin{aligned} \mathbb{E}\{X_i X_j X_k\} = & -\mathbb{E}\{X_i X_j\}\mathbb{E}\{X_k\} - \mathbb{E}\{X_j X_k\}\mathbb{E}\{X_i\} \\ & -\mathbb{E}\{X_k X_i\}\mathbb{E}\{X_j\} + 2\mathbb{E}\{X_i\}\mathbb{E}\{X_j\}\mathbb{E}\{X_k\} \end{aligned}$$

- Higher moments are easy to derive with a moment generating function:

$$M_{\mathbf{x}}(\mathbf{t}) = \exp\left(\mu^T \mathbf{t} + \frac{1}{2} \mathbf{t}^T \boldsymbol{\Sigma} \mathbf{t}\right),$$

$$\mathbb{E}\{x_1^{n_1} \dots x_4^{n_4}\} = \left. \frac{d^{n_1 + \dots + n_4}}{dx_1^{n_1} \dots dx_4^{n_4}} M_x(\mathbf{t}) \right|_{\mathbf{t}=\mathbf{0}}.$$

## Many other closures are possible:

---

- If one assumes that the distributions are Log-Normal, a different closure is used:

$$\mathbb{E}[X_i X_j X_k] = \frac{\mathbb{E}[X_i X_j] \mathbb{E}[X_j X_k] \mathbb{E}[X_i X_k]}{\mathbb{E}[X_i] \mathbb{E}[X_j] \mathbb{E}[X_k]}.$$

- One of the most common closures is the Linear Noise Approximation.
- In this, all moments are written in terms of themselves and lower moments:
  - ▶ the mean is set equal to the deterministic process.
  - ▶ the second moments are assumed to be gaussian, and depend upon the mean and itself.

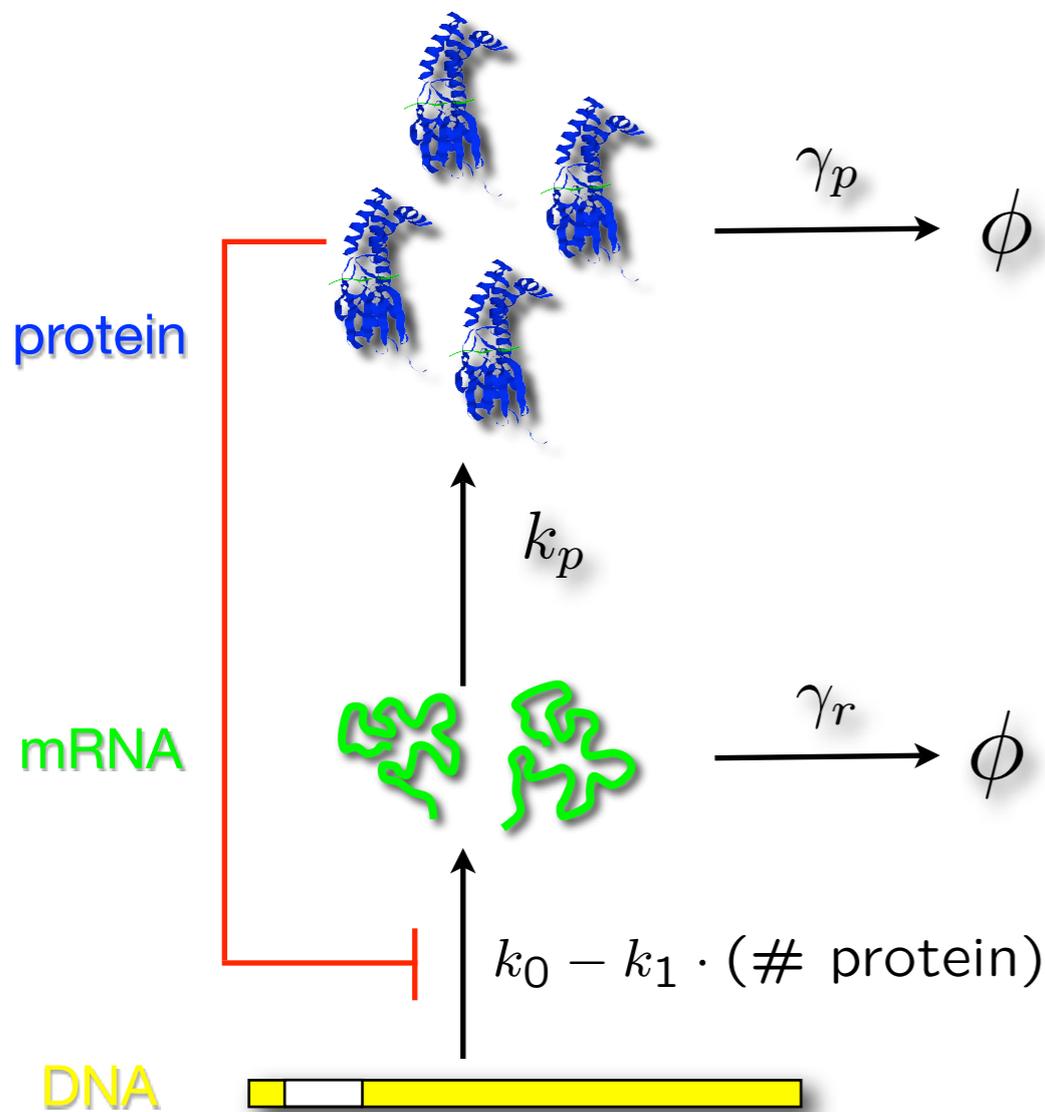
$$\frac{d}{dt} \begin{bmatrix} \{\mu_i\} \\ \{\sigma_{ij}\} \end{bmatrix} = \begin{bmatrix} f_1(\{\mu_i\}) \\ f_2(\{\mu_i, \{\sigma_{ij}\}\}) \end{bmatrix},$$

# Noise Suppression and Exploitation (Examples)

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- Feedback for Noise Suppression
- Stochastic Focussing
- Stochastic Switches

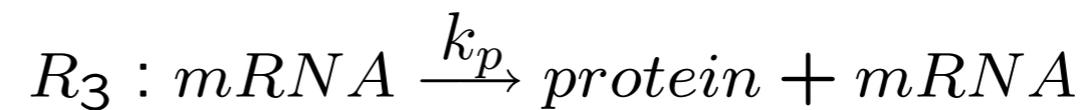
# Noise Attenuation through Negative Feedback



## Reactants

$X_1(t)$  is # of mRNA;  $X_2(t)$  is # of protein

## Reactions



## Stoichiometry and Propensity

$$S = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

$$w(X) = \begin{bmatrix} k_0 - k_1 X_2 \\ \gamma_r X_1 \\ k_p X_1 \\ \gamma_p X_2 \end{bmatrix} = \underbrace{\begin{bmatrix} 0 & -k_1 \\ \gamma_r & 0 \\ k_p & 0 \\ 0 & \gamma_p \end{bmatrix}}_W \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} + \underbrace{\begin{bmatrix} k_0 \\ 0 \\ 0 \\ 0 \end{bmatrix}}_{w_0}$$

## Steady-State Moments

$$A = SW = \begin{bmatrix} -\gamma_r & -k_1 \\ k_p & -\gamma_p \end{bmatrix}, \quad Sw_0 = \begin{bmatrix} k_0 \\ 0 \end{bmatrix}$$

$$\bar{X} = -A^{-1}Sw_0 = \begin{bmatrix} \frac{k_0}{\gamma_r} \\ 1 + \frac{k_1 k_p}{\gamma_p \gamma_r} \\ \frac{k_0 k_p}{\gamma_r \gamma_p} \\ 1 + \frac{k_1 k_p}{\gamma_p \gamma_r} \end{bmatrix} =: \begin{bmatrix} \mu_r \\ \mu_p \end{bmatrix}$$

## Steady-State Covariance

$$BB^T = S \operatorname{diag}(W \bar{X} + w_0) S^T = \begin{bmatrix} k_0 + \gamma_r \mu_r - k_1 \mu_p & 0 \\ 0 & k_p \mu_r + \gamma_p \mu_p \end{bmatrix}$$

The steady-state covariances equation

$$A\bar{\Sigma} + \bar{\Sigma}A^T + BB^T = 0 \quad \text{Lyapunov Equation}$$

can be solved algebraically for  $\bar{\Sigma}$ .

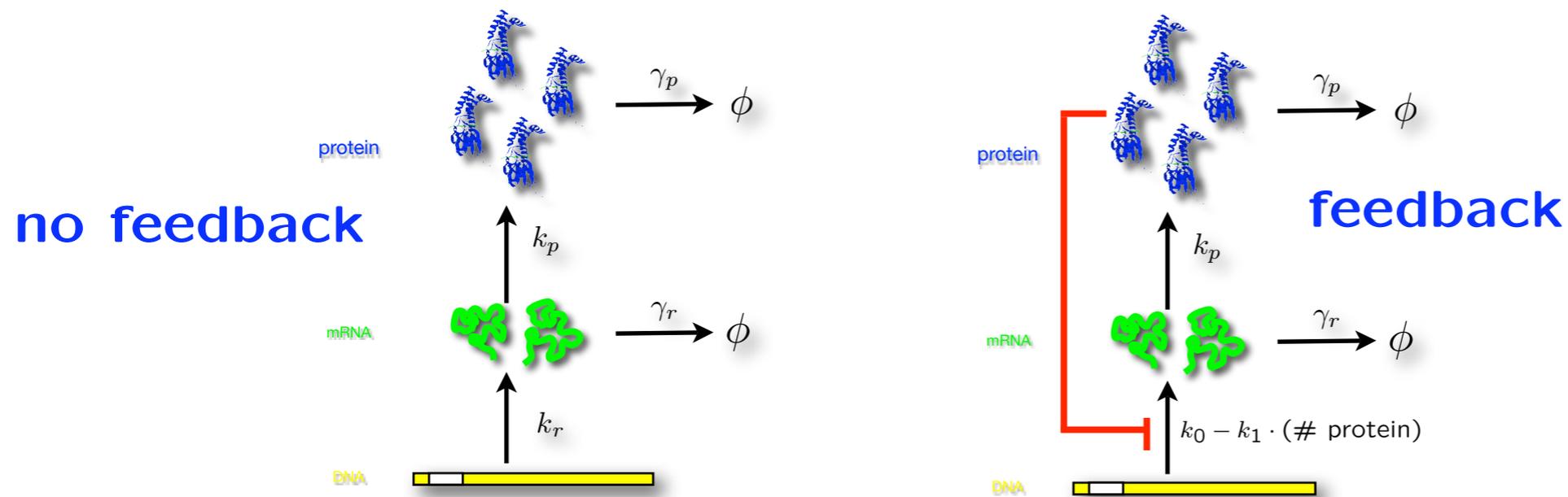
$$\bar{\Sigma}_{22} = \sigma_p^2 = \left[ \frac{1 - \phi}{1 + b\phi} \cdot \frac{b}{1 + \eta} + 1 \right] \mu_p \quad \text{where } \phi = \frac{k_1}{\gamma_p}, \quad b = \frac{k_p}{\gamma_r}, \quad \eta = \frac{\gamma_p}{\gamma_r}$$

## Feedback vs. No Feedback

In order to compare the noise in the two cases, we must ensure that **both configurations have the same mean!**

Impose the constraint:  $\mu_p^{FB} = \mu_p^{NFB} =: \mu_p^*$

This may be achieved by choosing  $k_0 = k_r + k_1 \mu_p^{NFB}$ .



Mean

$$\mu_p^*$$

$$\mu_p^*$$

Variance

$$\left[ \frac{b}{1 + \eta} + 1 \right] \mu_p^*$$

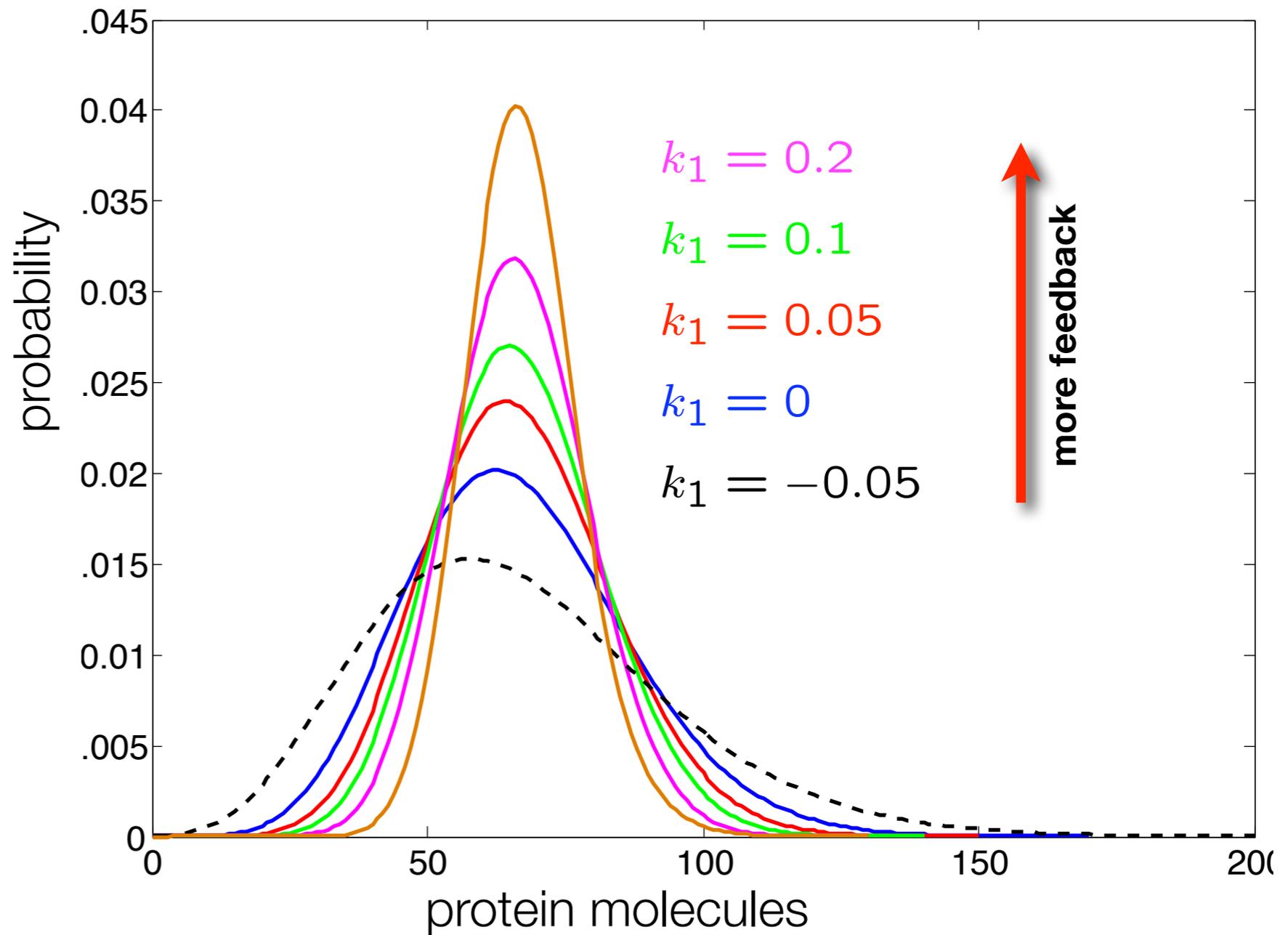
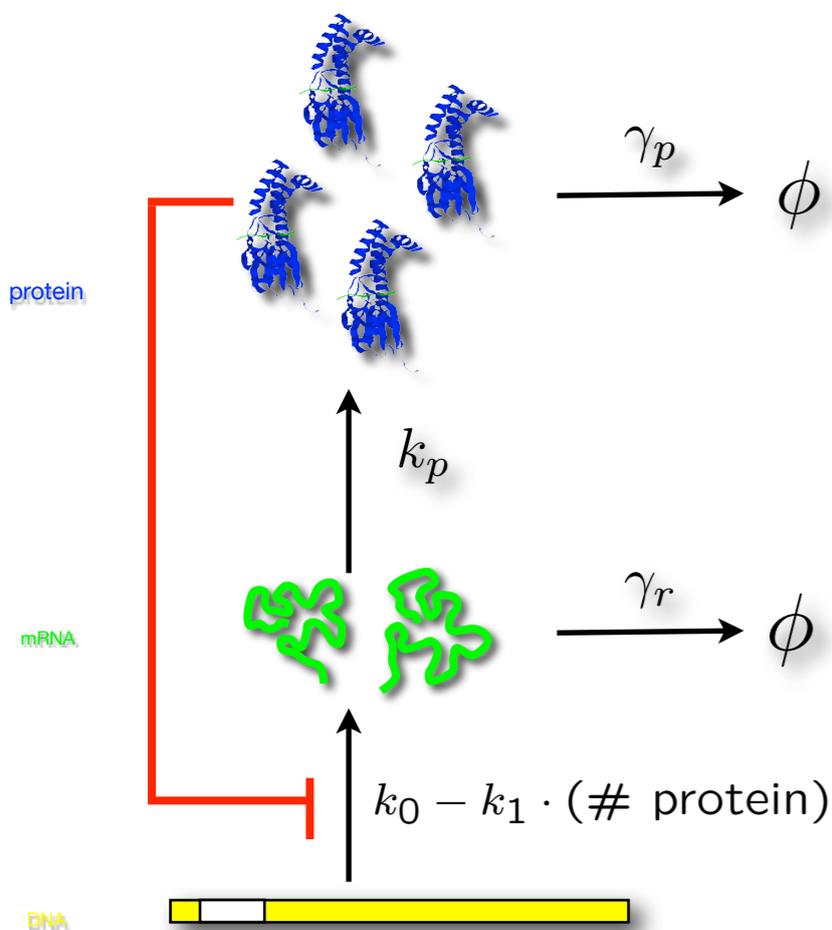
$$\left[ \frac{1 - \phi}{1 + b\phi} \cdot \frac{b}{1 + \eta} + 1 \right] \mu_p^* < 1$$

where  $\phi = \frac{k_1}{\gamma_p}$

**Protein variance is always smaller with negative feedback!**

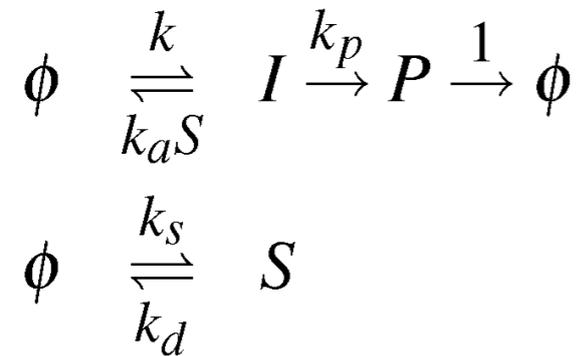
# Example

$$\gamma_p = \gamma_r = 1 \quad k_p = 10;$$



Note that these distributions are NOT Gaussian.

# Exploiting the Noise: Failure of the linear noise approximation



may be approximated by



$$q = \frac{1}{1 + \frac{n}{\Omega K}} \quad K = k_p/k_a$$

n is #S

**convex**

From Jensen's Inequality:

$$E[q] = E\left[\frac{1}{1 + \frac{n}{\Omega K}}\right] \geq \frac{1}{1 + \frac{E[n]}{\Omega K}}$$

- Noise *enhances* signal!

